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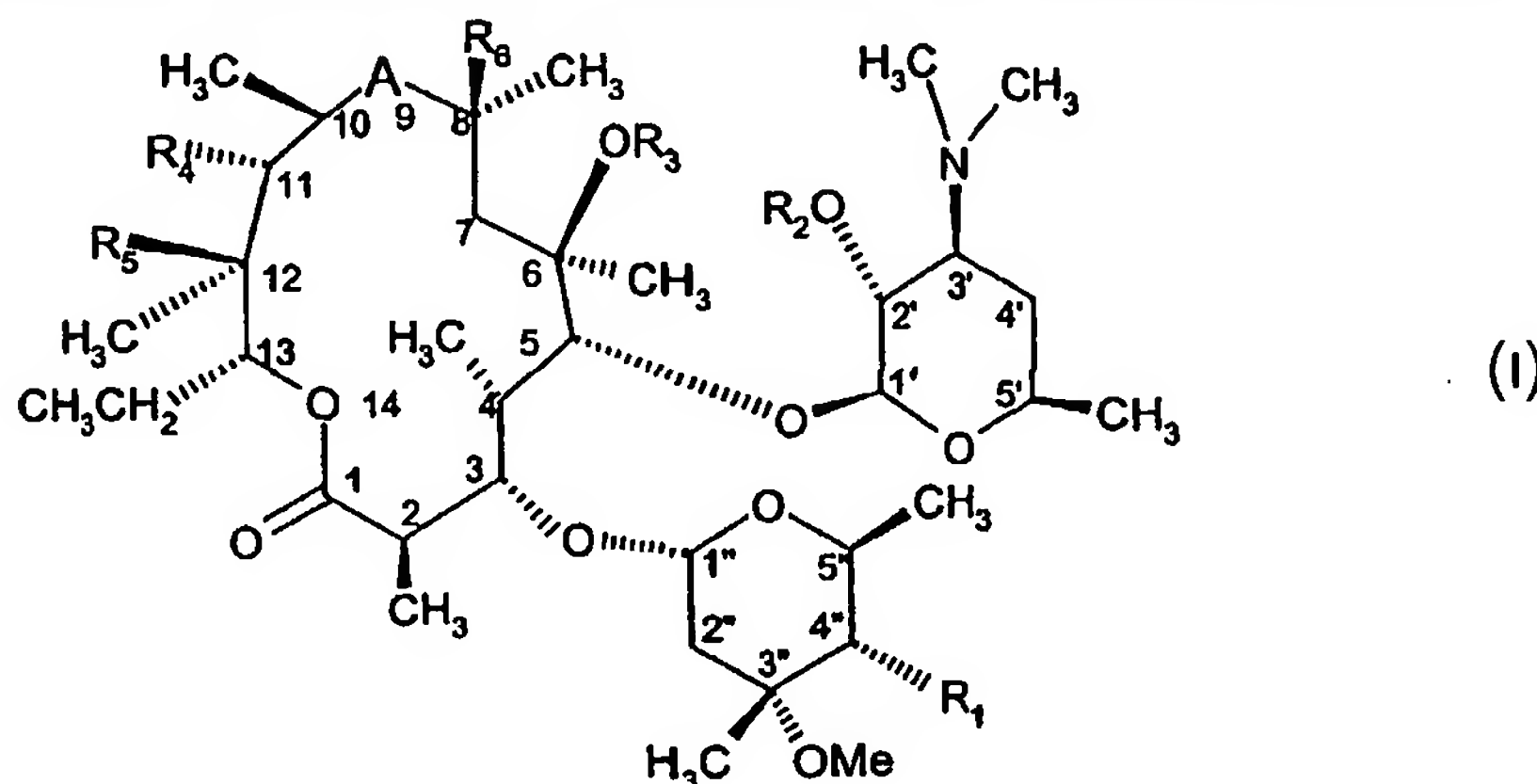
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[Continued on next page]

(54) Title: MACROLIDES



(57) Abstract: The present invention relates to 14 or 15 membered macrolides substituted at the 4" position of formula (I) and pharmaceutically acceptable salts and solvates thereof, to processes for their preparation and their use in therapy or prophylaxis of systemic or topical bacterial infections in a human or animal body.



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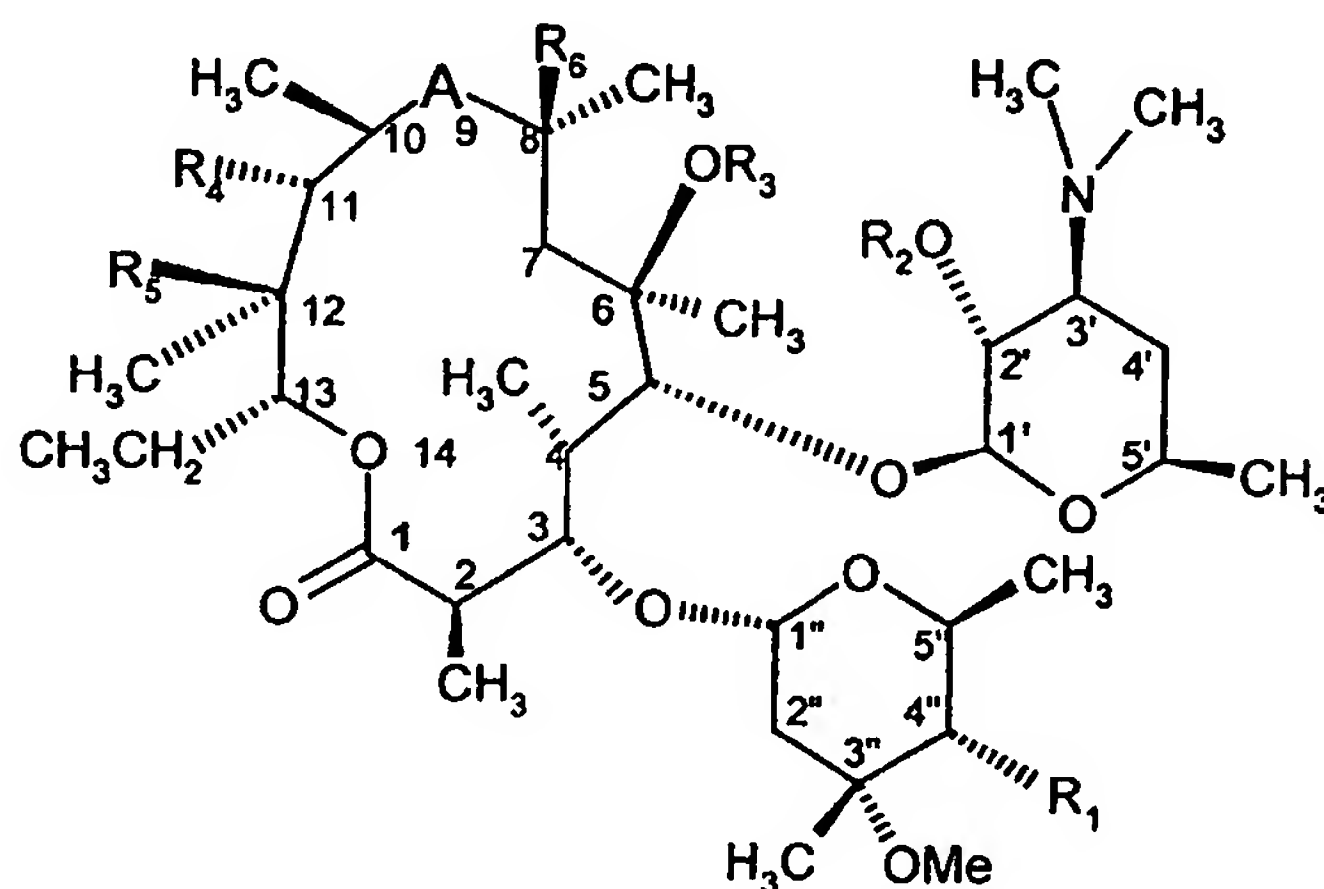
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Macrolides

The present invention relates to novel semi synthetic macrolides having antibacterial activity. More particularly this invention relates to 14 or 15 membered macrolides substituted at the 4'' position, to processes for their preparation, to compositions containing them and to their use in medicine.

Thus, the present invention provides compounds of general formula (I)



(I)

wherein:

A is a bivalent radical selected from:

-C(O)-, -C(O)NH-, -NHC(O)-, -N(CH₃)-CH₂-, -CH₂-N(CH₃)- or
-C(NOCH₂OCH₂CH₂OCH₃)-;

R₁ is OC(O)(CH₂)_nXR₇;

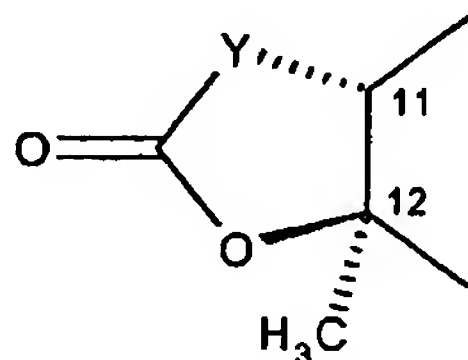
R₂ is hydrogen or a hydroxyl protecting group;

R₃ is hydrogen, C₁₋₄alkyl or C₃₋₆alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl;

R₄ is hydroxy or C₃₋₆alkenyloxy optionally substituted by 9 to 10 membered fused bicyclic heteroaryl;

R₅ is hydroxy or

R₄ and R₅ taken together with the intervening atoms form a cyclic group having the following structure:

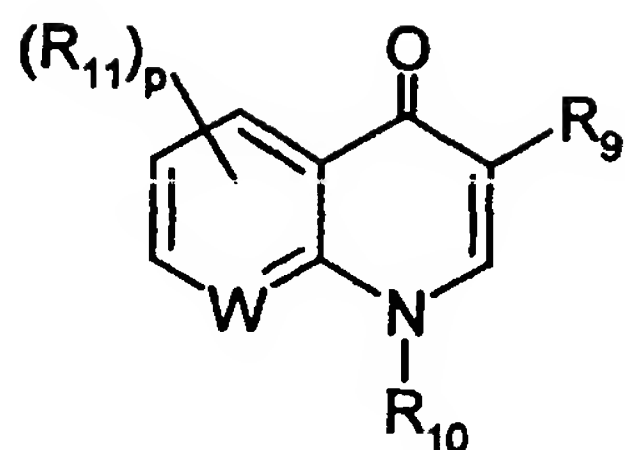


wherein Y is a bivalent radical selected from:

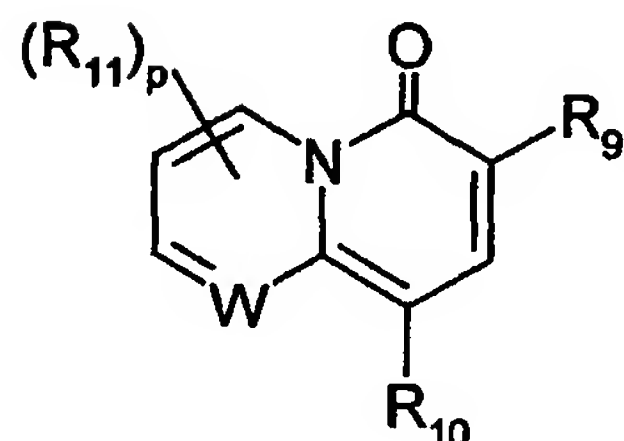
-CH₂-, -CH(CN)-, -O-, -N(R₈)- and -CH(SR₈)-;

R₆ is hydrogen or fluorine;

R₇ is a heterocyclic group having the following structures:



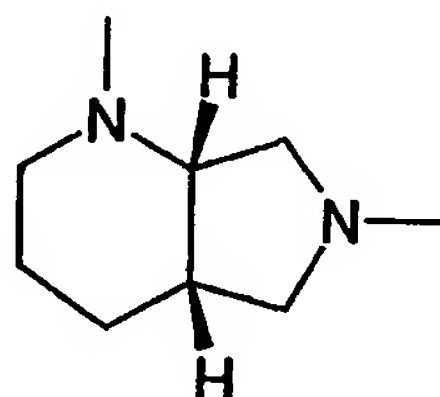
or



- 5 R_8 is hydrogen or C_{1-4} alkyl substituted by a group selected from:
 optionally substituted phenyl,
 optionally substituted 5 or 6 membered heteroaryl,
 optionally substituted 9 to 10 membered fused bicyclic heteroaryl;
 R_9 is hydrogen, $C(O)OR_{12}$, $C(O)NHR_{12}$ or $C(O)CH_2NO_2$;
 10 R_{10} is hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, optionally substituted phenyl or benzyl;
 R_{11} is halogen, C_{1-4} alkyl, C_{1-4} thioalkyl, C_{1-4} alkoxy, NH_2 , $NH(C_{1-4}alkyl)$ or $N(C_{1-4}alkyl)_2$;
 R_{12} is hydrogen or C_{1-4} alkyl;
 R_{13} is hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, optionally substituted phenyl or benzyl, acetyl
 15 or benzoyl;
 X is $-U(CH_2)_mZ-$ or X is a group selected from:



or



20

- U and Z independently are a divalent radical selected from:
 $-N(R_{13})-$, $-O-$, $-S(O)_q-$, $-N(R_{13})C(O)-$, $-C(O)N(R_{13})-$, $-N[C(O)R_{13}]-$,
 W is a carbon or a nitrogen atom;
 n is 0 or an integer from 1 to 5;
 25 m is an integer from 2 to 8;
 p is 0, 1 or 2;
 q is 0, 1 or 2;
 and pharmaceutically acceptable salts and solvates thereof.

Suitable pharmaceutically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic or inorganic acids, for example hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, acetates, citrates, succinates, tartrates, fumarates and maleates.

The solvates may, for example, be hydrates.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable acid addition salts together with pharmaceutically acceptable solvates.

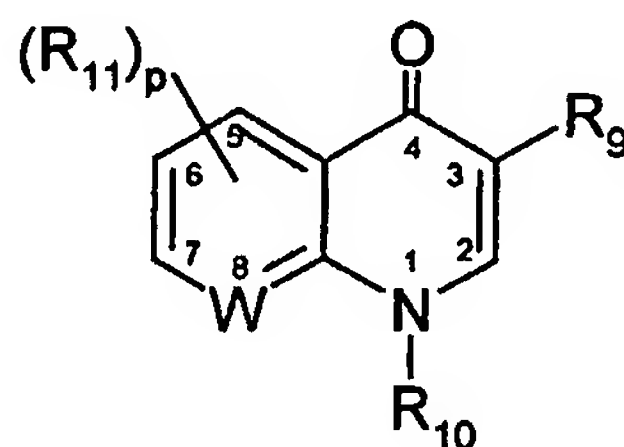
The compound of formula (I) and salts thereof may form solvates (e.g. hydrates) and the invention includes all such solvates.

In the general formula (I) as drawn the solid wedge shaped bond indicates that the bond is above the plane of the paper. The broken bond indicates that the bond is below the plane of the paper.

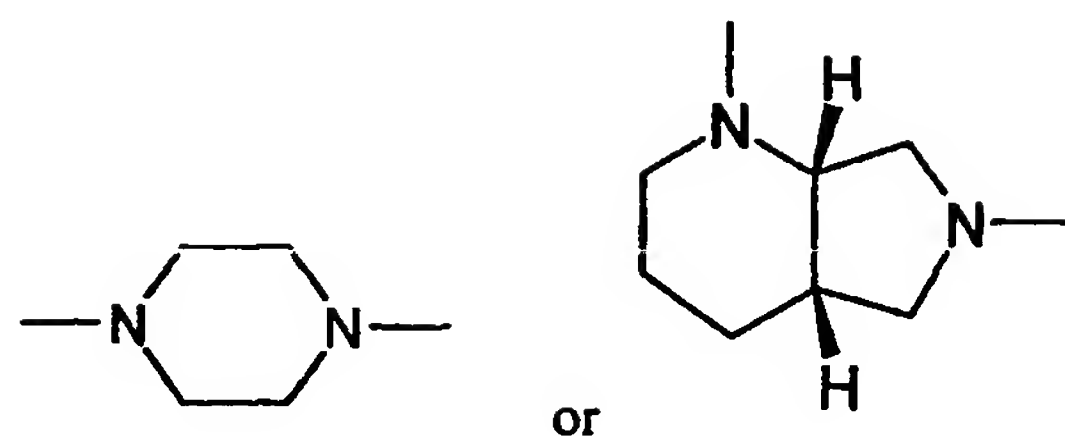
Compounds wherein R_2 represents a hydroxyl protecting group are in general intermediates for the preparation of other compounds of formula (I).

When the group OR_2 is a protected hydroxyl group this is conveniently an ether or an acyloxy group. Examples of particularly suitable ether groups include those in which R_2 is a trialkylsilyl (i.e. trimethylsilyl). When the group OR_2 represents an acyloxy group, then examples of suitable groups R_2 include acetyl or benzoyl.

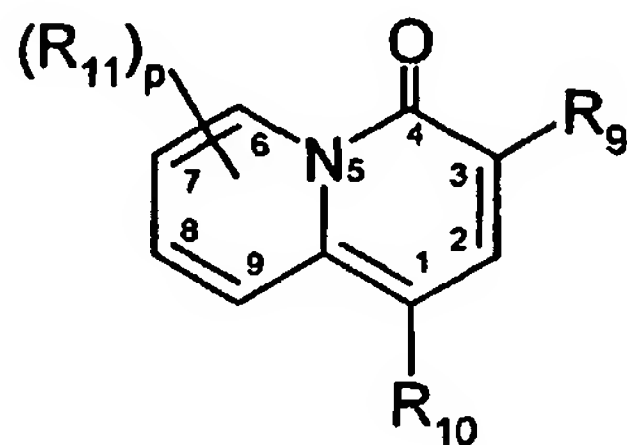
When R_7 is a heterocyclic group having the following structure:



wherein W is carbon or nitrogen, said heterocyclic is linked in the 7 or 6 position to the Z group as above defined or to one of the nitrogen atoms contained in the following structures:

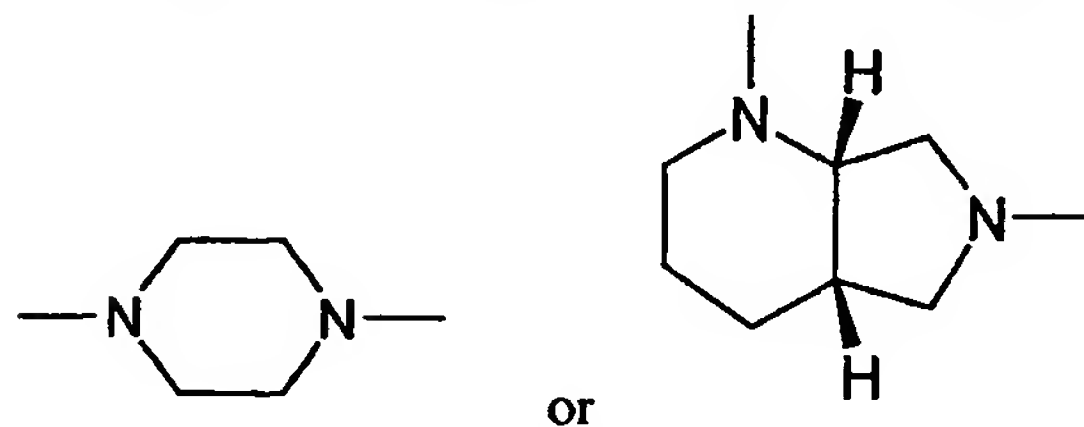


When R₇ is a heterocyclic group having the following structure:



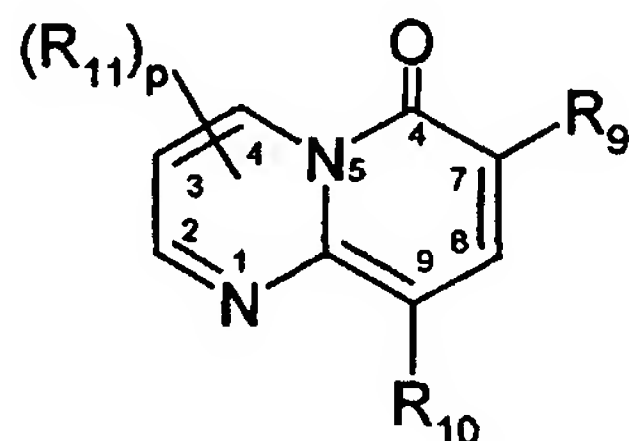
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said heterocyclic is linked in the 8 or 7 position to the Z group as above defined or to one of the nitrogen atoms contained in the following structures:

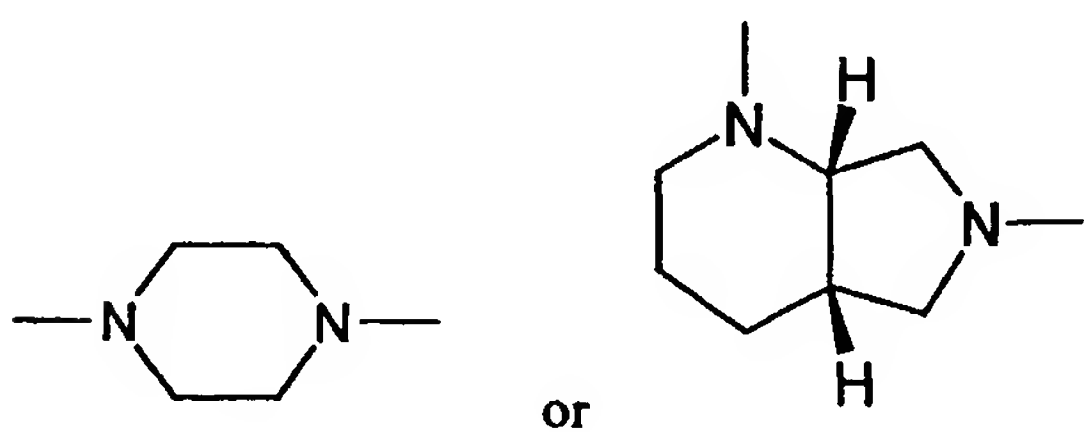


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When R₇ is a heterocyclic group having the following structure:



15 said heterocyclic is linked in the 2 or 3 position to the Z group as above defined or to one of the nitrogen atoms contained in the following structures:



The term C₁₋₄alkyl as used herein as a group or a part of the group refers to a straight or branched alkyl group containing from 1 to 4 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl.

- 5 The term C₂₋₆alkenyl group as used herein as a group or a part of the group refers to a straight or branched alkenyl group containing from 2 to 6 carbon atoms; examples of such groups include 2-propenyl, 1-propenyl, isopropenyl, 2-butenyl, 2-pentenyl, 2-hexenyl and the like. It will be appreciated that in groups of the form -O-C₂₋₆alkenyl, the double bond is preferably not adjacent to the oxygen.

10

The term C₃₋₇cycloalkyl group means a non-aromatic monocyclic hydrocarbon ring of 3 to 7 carbon atoms such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

- 15 The term 5 or 6 membered heteroaryl as used herein as a group or a part of the group refers to furanyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridyl, pyridinium, pyridazinyl or pyrimidinyl.

The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

20

The term C₁₋₄alkoxy group may be a straight chain or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy.

- 25 The term 9 to 10 membered fused bicyclic heteroaryl as used herein as a group or a part of the group refers to quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, benzofuranyl, benzimidazolyl, benzothienyl, benzoxazolyl, 1,3-benzodioxazolyl, indolyl, benzothiazolyl, furylpyridine, oxazolopyridyl or benzothiophenyl.

- 30 The terms optionally substituted phenyl, optionally substituted 5 or 6 membered heteroaryl or optionally substituted 9 to 10 membered fused bicyclic heteroaryl refer to a group which is substituted by 1 to 3 groups selected from:

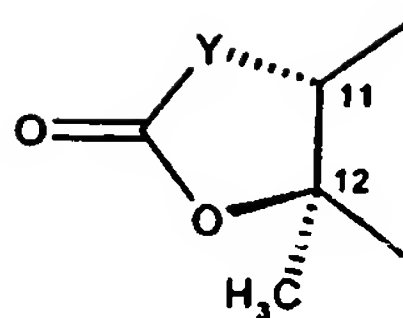
halogen, C₁₋₄alkyl, C₁₋₄alkoxy, hydroxy, nitro, cyano, amino, C₁₋₄alkylamino or diC₁₋₄alkylamino, phenyl or 5 or 6 membered heteroaryl.

- 35 Preferred compounds of formula (I) are those wherein R₂ is hydrogen.

In one embodiment, R₃ is hydrogen or C₁₋₄alkyl, for example methyl, ethyl or propyl.

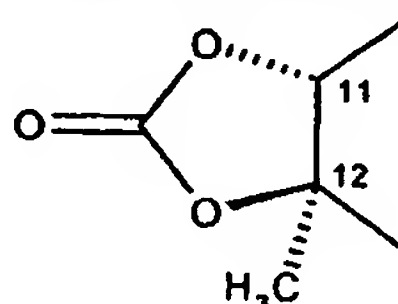
- 40 When A is -C(O)-, R₆ is preferably hydrogen and R₃ is preferably C₁₋₄alkyl (i.e. methyl) or R₆ is preferably fluorine and R₃ is preferably hydrogen.

When A is -C(O)-, R₄ and R₅ are preferably hydroxy or R₄ and R₅ taken together with the intervening atoms form a cyclic group having the following structure:



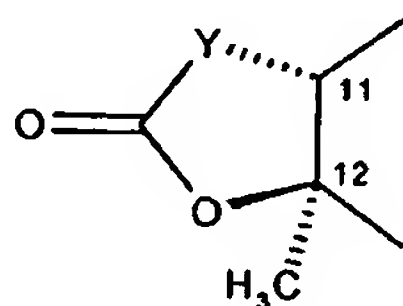
wherein Y is preferably $-N(R_8)-$ and R_8 is hydrogen or C_{1-4} alkyl such as methyl or ethyl.

- 5 When A is $-NHC(O)-$, $-C(O)NH-$, $-N(CH_3)-CH_2-$, $-CH_2-N(CH_3)-$ or $-C(NOCH_2OCH_2CH_2OCH_3)-$ and R_4 or R_5 is hydroxy or R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:



- 10 R_6 is preferably hydrogen and R_3 is preferably hydrogen, C_{1-4} alkyl (i.e. methyl) or 2-propenyl.

When A is $-NHC(O)-$, $-C(O)NH-$, $-N(CH_3)-CH_2-$, $-CH_2-N(CH_3)-$ or $-C(NOCH_2OCH_2CH_2OCH_3)-$ and R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:

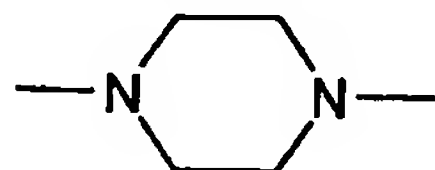


- 15 wherein Y is a bivalent radical selected from $-CH_2-$, $-CH(CN)-$, $-N(R_8)-$, R_6 is preferably hydrogen and R_3 is preferably C_{1-4} alkyl (i.e. methyl) or 2-propenyl.

When n is 0, U is preferably selected from $-N(R_{13})-$, $-O-$ and $-S-$.

- 20 In the compounds of formula (I) n is preferably 1 or 2. Within this class, compounds wherein n is 2 are particularly preferred.

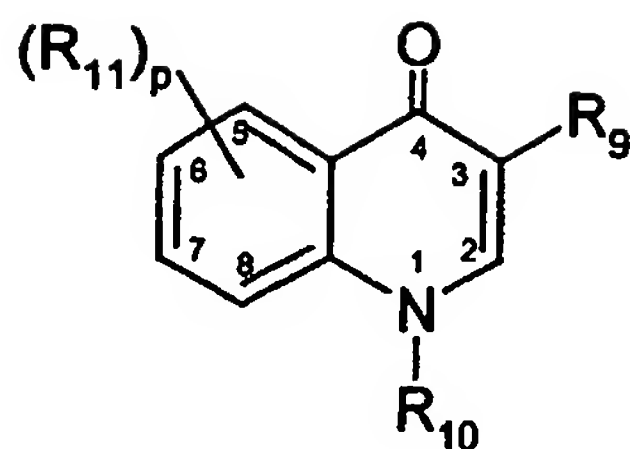
Preferred class of compounds of formula (I) are those wherein X is $NH(CH_2)_{2-5}NH$ or



- 25 ; within this class, compounds in which X is $NH(CH_2)_{2-3}NH$ are particularly preferred.

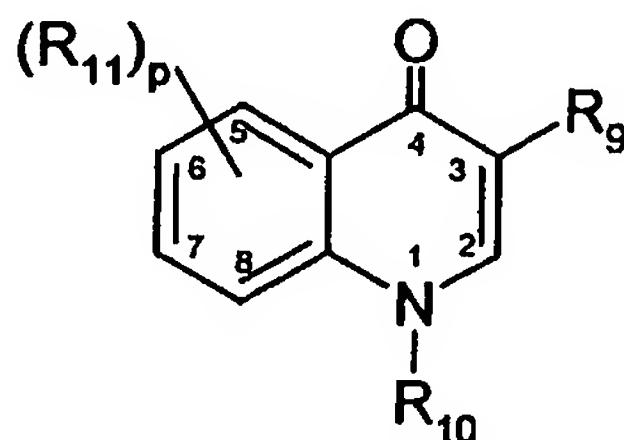
Another preferred class of compounds of formula (I) are those wherein X is $N(R_{13})(CH_2)_{2-3}NH$ and R_{13} is C_{1-4} alkyl such as methyl, or acetyl.

- 30 A further preferred class of compounds of formula (I) is that wherein R_7 is a heterocyclic of the following formula:



Within this class of compounds, those compounds wherein p is 0 or 1, R_{11} is halogen (i.e. chloro or fluoro) at position 6 or 7, R_9 is carboxy and R_{10} is methyl, ethyl or cyclopropyl are particularly preferred.

A particular preferred class of compounds according to the invention are those wherein R_2 is hydrogen, X is $NH(CH_2)_{2-3}NH$, R_7 is a heterocyclic group of the following formula:

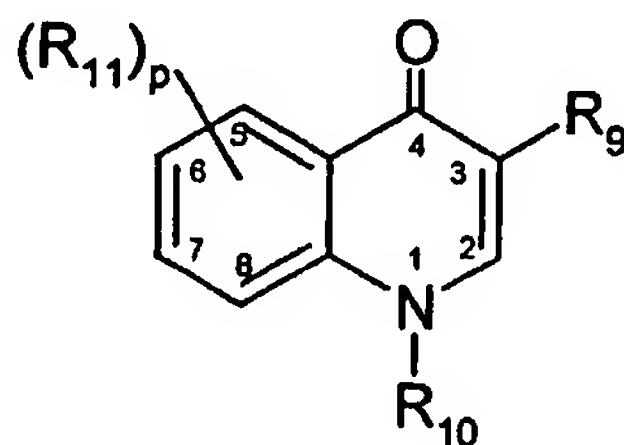


wherein p is 0 or 1, R_{11} is halogen (i.e. chloro or fluoro) at position 6 or 7, R_9 is carboxy and R_{10} is ethyl or cyclopropyl.

Another preferred class of compounds are those wherein R_9 is $C(O)OR_{12}$ and R_{12} is C_{1-4} alkyl, in particular methyl.

A further preferred class of compounds are those wherein R_{11} is C_{1-4} alkoxy, for example methoxy at position 8.

When R_3 is C_{3-6} alkenyl substituted by 9 to 10 membered fused bicyclic heteroaryl, 9 to 10 membered fused bicyclic heteroaryl is preferably 2-quinolyl or 3-quinolyl, R_4 and R_5 are preferably hydroxy and R_6 is hydrogen. Within this class of compounds, the compounds in which R_2 is hydrogen, X is $NH(CH_2)_{2-3}NH$, R_7 is a heterocyclic of the following formula:



wherein p is 1, R_{11} is halogen (i.e. chloro or fluoro) at position 6 or 7, R_9 is carboxy and R_{10} is ethyl or cyclopropyl are particularly preferred.

In one embodiment, Y is a bivalent radical selected from -CH₂-, -CH(CN)-, -O- and -N(R_g)-

Particularly preferred compounds of the invention are:

- 5 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyloxy)amino]ethyl]amino]propionyl]-8a-aza-8a-homoerythromycin A;
- 4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyloxy)amino]ethyl]amino]propionyl]-8a-aza-8a-homoerythromycin A;
- 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A;
- 10 4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A;
- 4''-O-[3-[[2-[(7-chloro-1-cyclopropyl-1,4-dihydro-3-methoxycarbonyl-4-oxo-6-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A;
- 15 4''-O-[3-[[2-[(3-carboxy-1,4-dihydro-1-ethyl-4-oxo-7-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A;
- 4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A ;
- 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-ethyl-8a-aza-8a-homoerythromycin A;
- 20 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-propyl-8a-aza-8a-homoerythromycin A;
- 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-9a-aza-9a-homoerythromycin A;
- 25 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyloxy)amino]ethyl]amino]propionyl]-11,12-dideoxy-6-O-methyl-11,12-(methylaminocarbonyloxy)-erythromycin A;
- 11,12-(aminocarbonyloxy)-4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyloxy)amino]ethyl]amino]propionyl]-11,12-dideoxy-6-O-methyl-erythromycin
- 30 A;
- 11,12-(aminocarbonyloxy)-4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyloxy)amino]ethyl]amino]propionyl]-11,12-dideoxy-6-O-methyl-erythromycin A;
- 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A;
- 35 4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A;
- 4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A;
- 4''-O-[3-[[2-[(3-carboxy-7-chloro-1,4-dihydro-1-ethyl-4-oxo-6-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A and 4''-O-[3-[[2-[(3-
- 40 carboxy-1,4-dihydro-1-ethyl-6-fluoro-4-oxo-7-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A;
- 4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A;

- (11*S*, 11*aR*)-11-(carboxycyanomethyl)-4''-O-[3-[[2-[(3-carboxy-1,4-dihydro-1-ethyl-4-oxo-7-quinoliny]amino]ethyl]amino]propionyl]-11-deoxy-6-*O*-methyl-erythromycin A;
 (11*S*, 11*aR*)-11-(carboxycyanomethyl)-4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinoliny]amino]ethyl]amino]propionyl]-11-deoxy-6-*O*-methyl-erythromycin A;
 5 (11*S*, 11*aR*)-4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinoliny]amino]ethyl]amino]propionyl]-11-(carboxycyanomethyl)-11-deoxy-6-*O*-methyl-erythromycin A;
 4''-O-[3-[4-(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinoliny]amino]ethyl]amino]propionyl]-roxithromycin;
 10 4''-O-[3-[4-(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinoliny]amino]ethyl]amino]propionyl]-roxithromycin;
 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-3-quinoliny]amino]ethyl]amino]propionyl]-azithromycin;
 11,12-carbonate-4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinoliny]amino]ethyl]amino]propionyl]-11,12 dideoxy azithromycin;
 15 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-3-quinoliny]amino]ethyl]amino]propionyl]-6-*O*-methyl-azithromycin;
 11,12-carbonate-4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinoliny]amino]ethyl]amino]propionyl]-11,12-dideoxy-azithromycin;
 20 11,12-carbonate-4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinoliny]amino]ethyl]amino]propionyl]-11,12 dideoxy azithromycin.

Further preferred compounds of the invention are:

- 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinoliny]amino]ethyl]amino]propionyl]-6-*O*-methyl-8*a*-aza-8*a*-homoerythromycin A;
 25 11,12-carbonate-4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinoliny]amino]ethyl]amino]propionyl]-11,12-dideoxy-azithromycin;
 11,12-carbonate-4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinoliny]amino]ethyl]amino]propionyl]-11,12 dideoxy azithromycin;
 30 11,12-carbonate-4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinoliny]amino]ethyl]amino]propionyl]-11,12-dideoxy-azithromycin;
 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinoliny]amino]ethyl]amino]propionyl]-azithromycin;
 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinoliny]amino]ethyl]amino]propionyl]-11,12-dideoxy-11,12-(ethylaminocarbonyloxy)-6-*O*-methyl-erythromycin A;
 35 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinoliny]amino]ethyl]amino]propionyl]-6-*O*-methyl-erythromycin A;
 4''-O-[3-[[2-[(3-carboxy-1,4-dihydro-1-ethyl-4-oxo-7-quinoliny]amino]ethyl]amino]propionyl]-6-*O*-methyl-erythromycin A;
 40 4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinoliny]amino]ethyl]amino]propionyl]-6-*O*-methyl-erythromycin A;
 4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinoliny]amino]ethyl]amino]propionyl]-6-*O*-methyl-erythromycin A;

- (11*S*, 11*aR*)-4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinoliny)amino]ethyl]amino]propionyl]-11-(carboxycyanomethyl)-11-deoxy-6-*O*-methyl-erythromycin A;
- (11*S*, 11*aR*)-11-(carboxycyanomethyl)-4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinoliny)amino]ethyl]amino]propionyl]-11-deoxy-6-*O*-methyl-erythromycin A;
- 4"-O-[3-[4-(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinoliny)amino]ethyl]amino]propionyl]-roxithromycin;
- 4"-O-(3-(2-(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinoliny)amino)ethyl)-methyl-amino)propionyl)-11,12-dideoxy-11,12-(ethylaminocarbonyloxy)-6-*O*-methylerythromycin A;
- 4"-O-{3-[(2-[(3-carboxymethyl-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinoliny)amino]ethyl)amino]propionyl}-6-*O*-methyl-erythromycin A;
- 11,12-(aminocarbonyloxy)-4"-O-{3-[(2-[(3-carboxy-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinoliny)amino]ethyl)amino]propionyl}-11,12-dideoxy-6-*O*-methyl-erythromycin A;
- 4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinoliny)amino]ethyl]-methyl-amino]propionyl]-azithromycin;
- 11,12-carbonate-4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinoliny)amino]ethyl]methylamino]propionyl]-11,12-dideoxy-azithromycin;
- 4"-O-(3-{[2-(7-chloro-1-cyclopropyl-3-methoxycarbonyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethyl]-amino}-propionyl)-azithromycin;
- 4"-O-(3-{[2-(7-chloro-1-cyclopropyl-3-methoxycarbonyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethyl]-methyl-amino}-propionyl)-azithromycin;
- 4"-O-{3-[(2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinoliny)amino]ethyl)methylamino]propionyl}-azithromycin; and
- 4"-O-[3-[[2-[(3-carboxy-1-ethyl-1,4-dihydro-4-oxo-6-quinoliny)amino]ethyl]amino]propionyl]-6-*O*-methyl-erythromycin A.

Compounds according to the invention also exhibit a broad spectrum of antibacterial activity against a wide range of clinical pathogenic microorganisms. For example, using a standard microtiter broth serial dilution test, compounds of the invention have been found to exhibit useful levels of activity against a wide range of pathogenic microorganisms including strains of *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella pneumophila*. The compounds of the invention may therefore be used for treating a variety of diseases caused by pathogenic bacteria in human beings and animals. The compounds of the invention may also be active against resistant strains, for example erythromycin resistant strains. In particular, the compounds of the invention may be active against erythromycin resistant strains of *Streptococcus pneumoniae* and *Streptococcus pyogenes*.

Thus, according to another aspect of the present invention, we provide a compound of formula (I) or a physiologically acceptable salt thereof for use in the therapy or prophylaxis of systemic or topical bacterial infections in a human or animal subject.

According to a further aspect of the invention we provide the use of a compound of formula (I) or a physiologically acceptable salt thereof for the manufacture of a therapeutic agent for the treatment or prophylaxis of systemic or topical bacterial infections in a human or animal body.

5

According to a yet further aspect of the invention we provide a method of treatment of the human or non-human animal body to combat bacterial infections which method comprises administering to the body an effective amount of a compound of formula (I) or a physiologically acceptable salt thereof.

10

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

15

The compounds of the invention may be formulated for administration in any convenient way for use in human or veterinary medicine and the invention therefore includes within its scope pharmaceutical compositions comprising a compound of the invention adapted for use in human or veterinary medicine. Such compositions may be presented for use in conventional manner with the aid of one or more suitable carriers or excipients. The compositions of the invention include those in a form especially formulated for parenteral, oral, buccal, rectal, topical, implant, ophthalmic, nasal or genito-urinary use.

20

The compounds according to the invention may be formulated for use in human or veterinary medicine by injection (e.g. by intravenous bolus injection or infusion or via intramuscular, subcutaneous or intrathecal routes) and may be presented in unit dose form, in ampoules, or other unit-dose containers, or in multi-dose containers, if necessary with an added preservative. The compositions for injection may be in the form of suspensions, solutions, or emulsions, in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, solubilising and/or dispersing agents. Alternatively the active ingredient may be in sterile powder form for reconstitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

25

30

The compounds of the invention may also be presented for human or veterinary use in a form suitable for oral or buccal administration, for example in the form of solutions, gels, syrups, mouth washes or suspensions, or a dry powder for constitution with water or other suitable vehicle before use, optionally with flavouring and colouring agents. Solid compositions such as tablets, capsules, lozenges, pastilles, pills, boluses, powder, pastes, granules, bullets or premix preparations may also be used. Solid and liquid compositions for oral use may be prepared according to methods well known in the art. Such compositions may also contain one or more pharmaceutically acceptable carriers and excipients which may be in solid or liquid form.

35

40

The compounds of the invention may also be administered orally in veterinary medicine in the form of a liquid drench such as a solution, suspension or dispersion of the active ingredient together with a pharmaceutically acceptable carrier or excipient.

- 5 The compounds of the invention may also, for example, be formulated as suppositories e.g. containing conventional suppository bases for use in human or veterinary medicine or as pessaries e.g. containing conventional pessary bases.

10 The compounds according to the invention may be formulated for topical administration, for use in human and veterinary medicine, in the form of ointments, creams, gels, lotions, shampoos, powders, (including spray powders), pessaries, tampons, sprays, dips, aerosols, drops (e.g. eye ear or nose drops) or pour-ons.

15 Aerosol sprays are conveniently delivered from pressurised packs, with the use of a suitable propellant, eg dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas.

20 For topical administration by inhalation the compounds according to the invention may be delivered for use in human or veterinary medicine via a nebuliser.

The pharmaceutical compositions for topical administration may also contain other active ingredients such as corticosteroids or antifungals as appropriate.

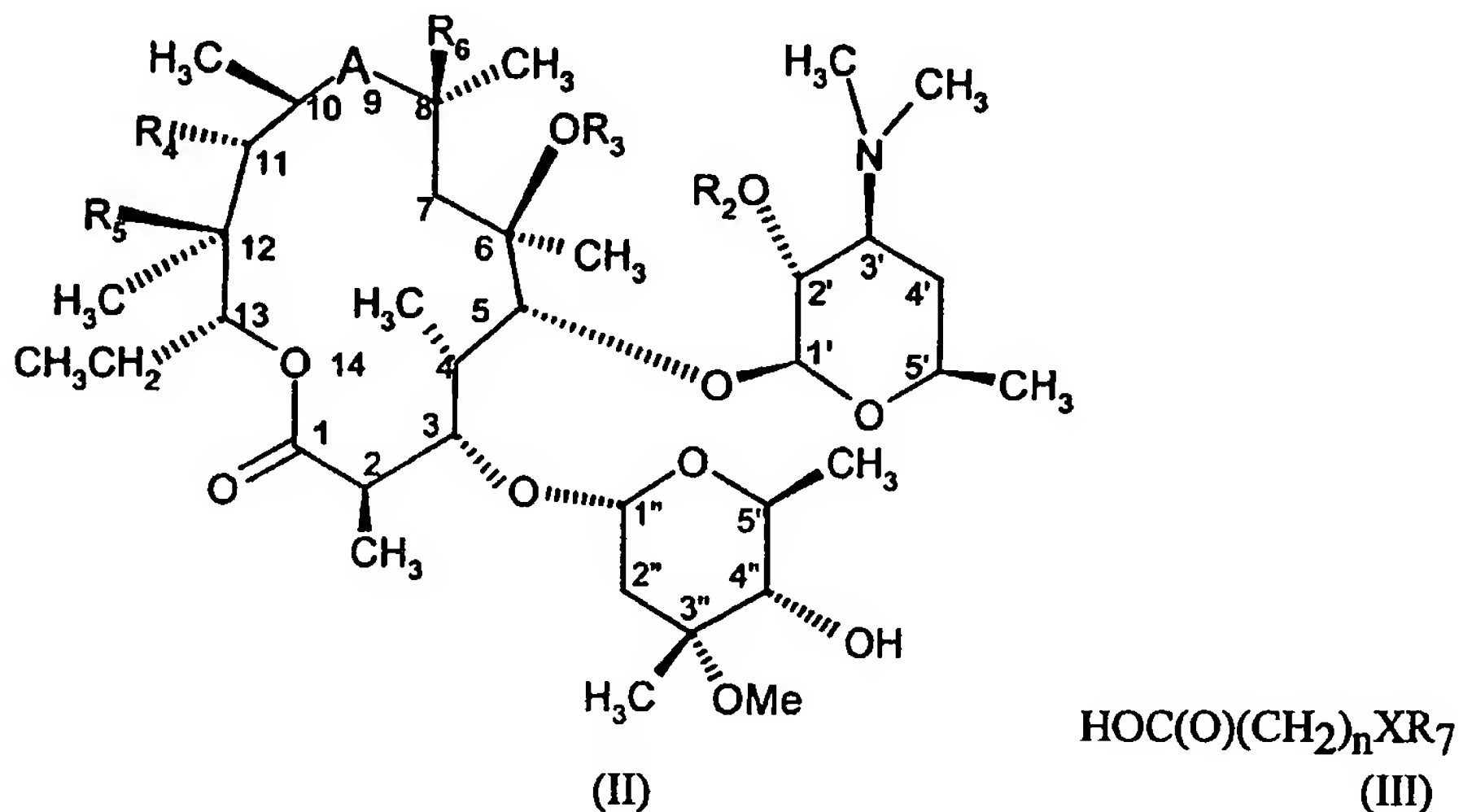
25 The compositions may contain from 0.01-99% of the active material. For topical administration, for example, the composition will generally contain from 0.01-10%, more preferably 0.01-1% of the active material.

30 For systemic administration the daily dose as employed for adult human treatment it will range from 2-100mg/kg body weight, preferably 5-60mg/kg body weight, which may be administered in 1 to 4 daily doses, for example, depending on the route of administration and the condition of the patient. When the composition comprises dosage units, each unit will preferably contain 200mg to 1g of active ingredient. The duration of treatment will be dictated by the rate of response rather than by arbitrary numbers of days.

35 Compounds of general formula (I) and salts thereof may be prepared by the general method outlined hereinafter. In the following description, the groups R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, A, X, Y, U, Z, W, n, m, p, and q have the meaning defined for the compounds of formula (I) unless otherwise stated. The groups XR₇ and ZR₇ are XR₇ and ZR₇ as defined for formula (I) or groups convertible to XR₇ and ZR₇ respectively.
40 Conversion of a group to a XR₇ or ZR₇ group typically arises if a protecting group is needed during the reactions described below. A comprehensive discussion of the ways in which such groups may be protected and methods for cleaving the resulting protected derivatives is given in for example T.W. Greene and P.G.M Wuts in Protective Groups in Organic Synthesis 2nd ed., John Wiley & Son, Inc 1991.

Compounds of formula (I) wherein n is an integer 1 to 5, may be prepared by reaction of 4'' hydroxy of formula (II) with a suitable activated derivative of the carboxylic acid (III), followed where necessary by subsequent removal of the hydroxyl protecting group R₂.

5



Suitable activated derivatives of the carboxyl group include the corresponding acyl halide, mixed anhydride or activated ester such as a thioester. The reaction is preferably carried out in a suitable aprotic solvent such as a halohydrocarbon (e.g. dichloromethane) or N,N-dimethylformamide optionally in the presence of a tertiary organic base such as dimethylaminopyridine or triethylamine or in the presence of inorganic base (i.e sodium hydride) and at a temperature within the range of 0° to 120°C.

15

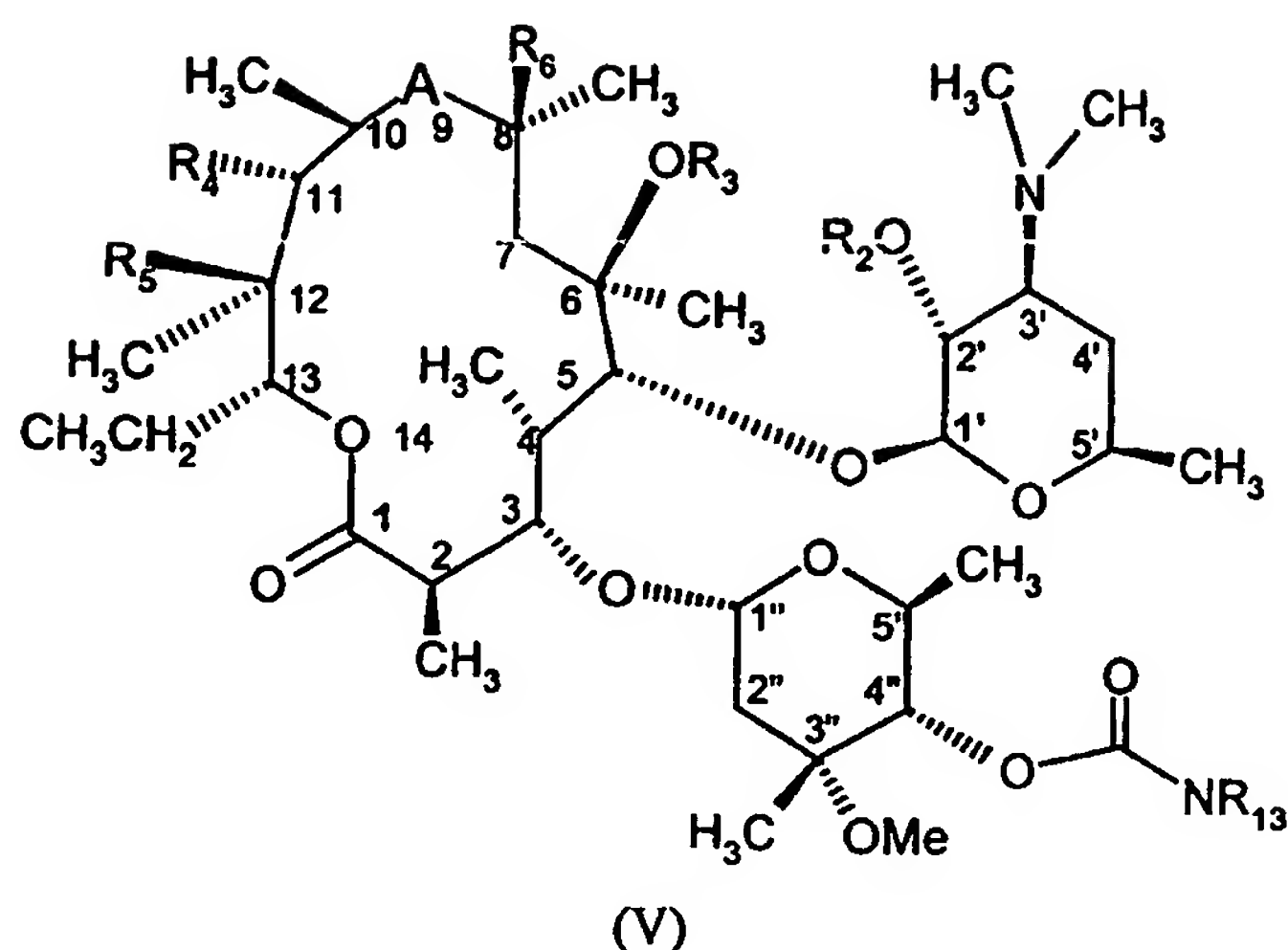
Compounds of formula (I) wherein n is 0, U is a group selected from:

-N(R₁₃)-, -O- and -S(O)_q- wherein q is 0,

may be prepared by reaction of compounds of formula (II), in which the 4'' hydroxy is suitable activated, with a compound of formula XR₇ (IV), followed where necessary by subsequent removal of the hydroxyl protecting group R₂. Suitable activated derivatives of the 4'' hydroxy group include for example carbonyl imidazole. The reaction is preferably carried out in a suitable aprotic solvent such as a halohydrocarbon (e.g. dichloromethane) or N,N-dimethylformamide optionally in the presence of a tertiary base such as dimethylaminopyridine or triethylamine and at a temperature within the range of 0° to 120°C.

25

Compounds of formula (I) wherein n is 0 and U is -N(R₁₃)C(O)-, may be prepared by reaction of compounds of formula (V),

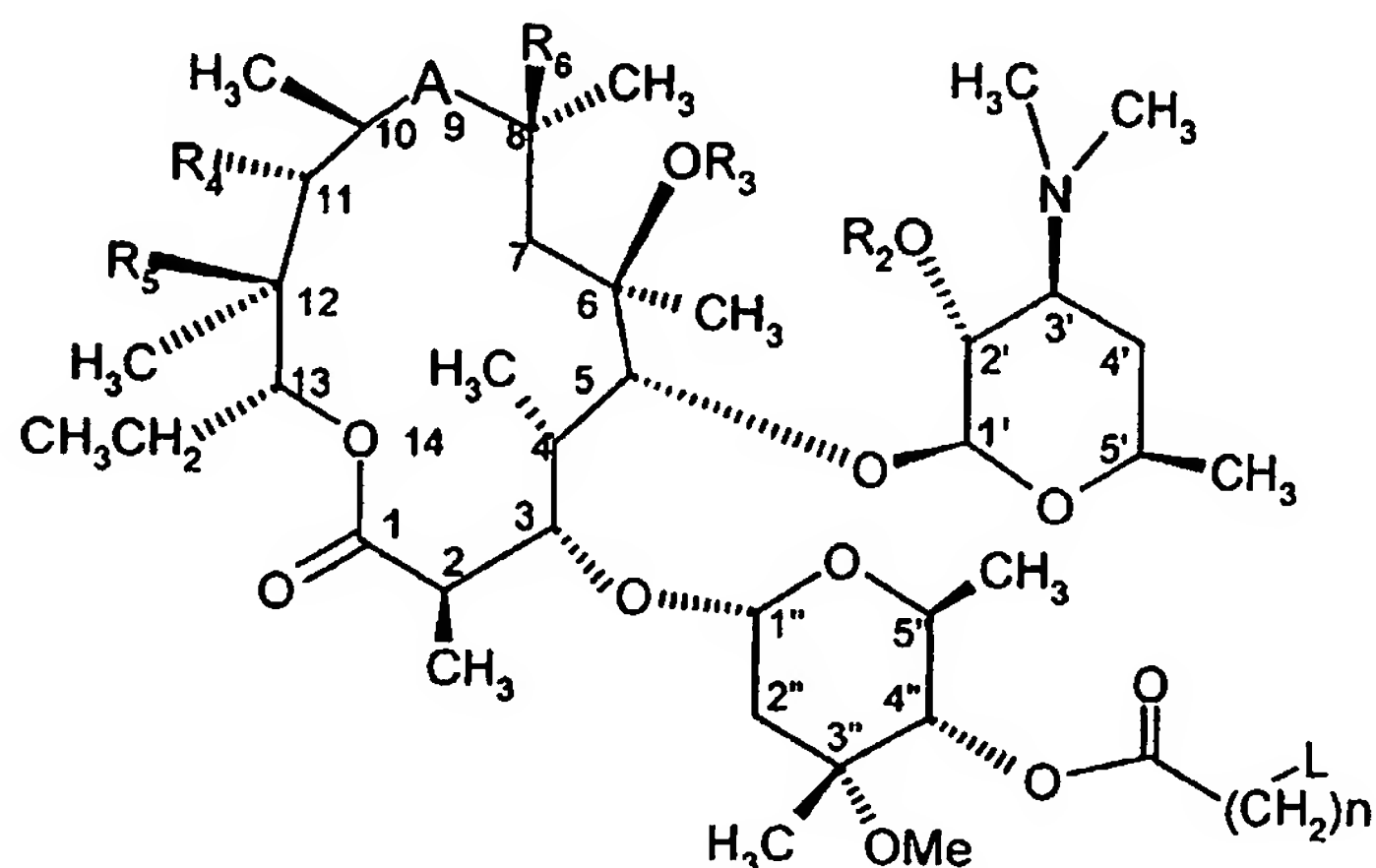


5 with a compound of formula $\text{HOC(O)C(O)(CH}_2\text{)}_m\text{ZR}_7\text{(VI)}$, followed where necessary by subsequent removal of the hydroxyl protecting group R_2 . The reaction is preferably carried out in a suitable aprotic solvent such as a halohydrocarbon (e.g. dichloromethane) or N,N-dimethylformamide optionally in the presence of a tertiary base such as dimethylaminopyridine or triethylamine and at a temperature within the range of 0° to 120°C .

10 Compounds of formula (V) may be prepared by treatment of compounds of formula (II), in which the $4''$ hydroxy is suitable activated, with amine $\text{NR}_{13}\text{(VIIa)}$. Suitable activated derivatives of the $4''$ hydroxy group include for example carbonyl imidazole.

15 Compounds of formula (I) wherein n is 0 and U is $-\text{C(O)N(R}_{13}\text{)}-$ may be prepared by reaction of $4''$ hydroxy of formula (II) with a suitable activated derivative of the carboxylic acid $\text{HOC(O)N(R}_{13}\text{)(CH}_2\text{)}_m\text{ZR}_7\text{(VIIb)}$ followed where necessary by subsequent removal of the hydroxyl protecting group R_2 .

20 In a preferred embodiment of the invention compounds of formula (I) wherein n is 1 to 5 and U is a group selected from $-\text{N(R}_{13}\text{)}-$, $-\text{O}-$, $-\text{S}-$, may be prepared by reaction of compounds of formula (VII),



(VII)

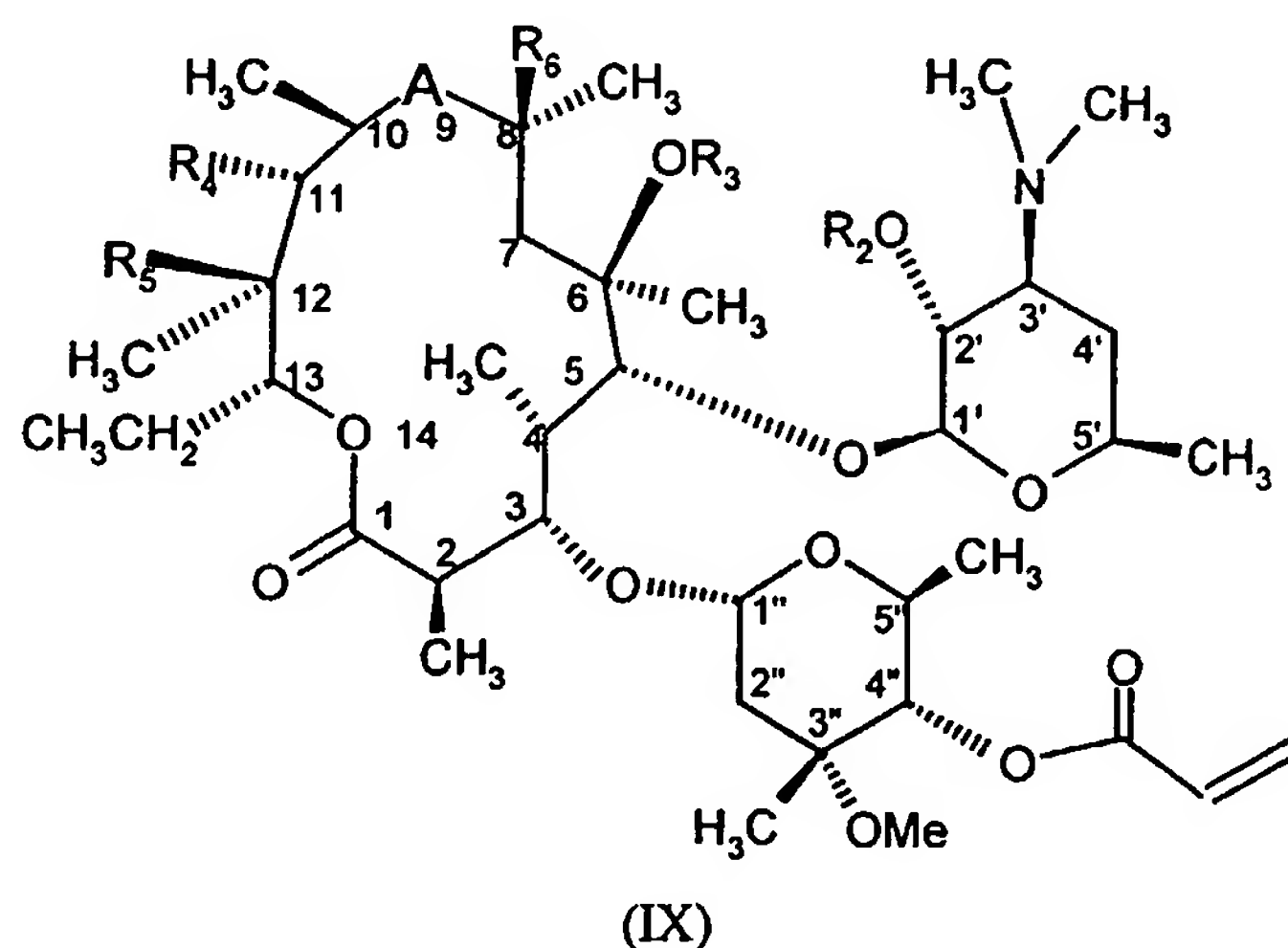
wherein n is an integer from 1 to 5 and L is a suitable leaving group, with XR_7 (IV) in which U is a group selected from $-N(R_{13})-$, $-O-$, $-S-$. The reaction is preferably carried out in a solvent such as a halohydrocarbon (e.g. dichloromethane), an ether (e.g. tetrahydrofuran, dimethoxyethane), acetonitrile or ethyl acetate and the like), dimethylsulphoxide, N,N-dimethylformamide, 1-methyl-pyrrolidone and in the presence of a base, followed, if desired, by removal of the hydroxyl protecting group R_2 . Examples of the bases which may be used include organic base such as diisopropylethylamine, triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, or inorganic base such as potassium hydroxide, cesium hydroxide, tetraalkylammonium hydroxyde, sodium hydride, potassium hydride and the like. Suitable leaving groups for this reaction include halogen (e.g. chlorine, bromine or iodine) or a sulfonyloxy group (e.g. tosyloxy or methanesulfonyloxy).

Compounds of formula (VII) may be prepared by reaction of a compound of formula (II), wherein R_2 is a hydroxyl protecting group; with a suitable activated derivative of the carboxylic acid $HOC(O)(CH_2)_nL$ (VIII), wherein L is a suitable leaving group as above defined. Suitable activated derivatives of the carboxyl group are those defined above for carboxylic acid (III). The reaction is carried out using the condition described above for the reaction of a compound of formula (II) with carboxylic acid (III).

In a further embodiment of the invention compounds of formula (I) of wherein n is 2, U is a group selected from:

$-N(R_{13})-$, $-O-$ and $-S-$,

may be prepared by Michael reaction of a compound of formula (IX), wherein R_2 is a hydroxyl protecting group



with a compound of formula XR_7 (IV). The reaction is suitably carried out in a solvent such as dimethylsulphoxide, N,N-dimethylformamide, 1-methyl-pyrrolidone, a halohydrocarbon (e.g. dichloromethane), an ether (e.g. tetrahydrofuran, dimethoxyethane), acetonitrile or ethyl

acetate or alcohol(e.g methanol, isopropanol) and the like and in the presence of a base, followed ,if desired, by removal of hydroxyl protecting group R₂.

Compounds of formula (I) may be converted into other compounds of formula (I). Thus
 5 compounds of formula (I) wherein U is -S(O)_q and q is 1 or 2 may be prepared by oxidation of the corresponding compound of formula (I) wherein q is 0. The oxidation is preferably carried out using a peracid, e.g. peroxybenzoic acid, followed by treatment with a phosphine, such as triphenylphosphine. The reaction is suitably carried out in an organic solvent such as methylene chloride.

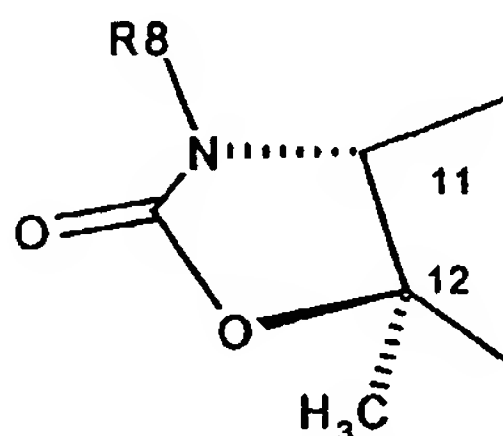
10

Compounds of formula (II) wherein A is -C(O)NH- or -NHC(O)-, R₄ or R₅ are hydroxy, R₃ is hydrogen and R₆ is hydrogen are known compounds or they may be prepared by analogous methods to those known in the art . Thus they can be prepared according to the procedures described in EP 507595 and EP 503932.

15

Compounds of formula (II), wherein A is -C(O)NH- or -NHC(O)-, R₄ or R₅ are hydroxy and R₃ is C₁₋₄alkyl or C₃₋₆alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl and R₆ is hydrogen are known compounds or they may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures
 20 described in WO 9951616 and WO 0063223.

Compounds of formula (II), wherein A is -C(O)NH- or -NHC(O)-, -N(CH₃)-CH₂-, -CH₂-N(CH₃)-, R₄ and R₅ taken together with the intervening atoms form a cyclic group having the following structure:

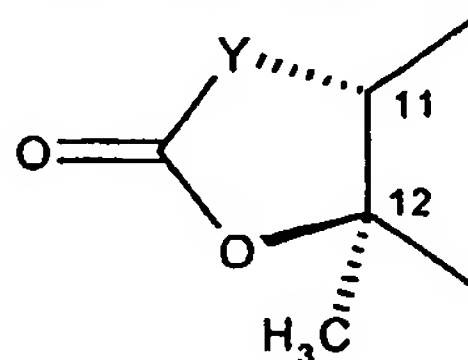


25

R₃ is C₁₋₄alkyl, or C₃₋₆alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl and R₆ is hydrogen are known compounds or they may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures described in USP N°6262030

30

Compounds of formula (II), wherein A is -C(O)-, R₄ or R₅ are hydroxy or R₄ and R₅ taken together with the intervening atoms form a cyclic group having the following structure:



wherein Y is a bivalent radical selected from:

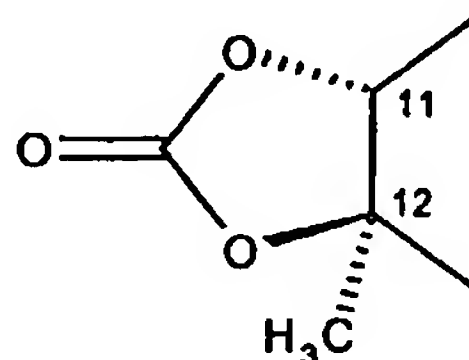
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-O- and -N(R_g)-

and R_3 is C_{1-4} alkyl, or C_{3-6} alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl are known compounds or they may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures described in EP 307177, EP 248279, WO 0078773, WO 9742204.

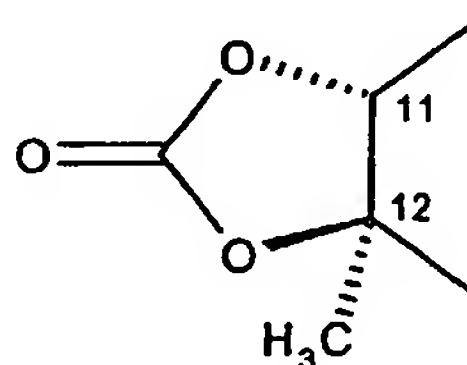
5

Compounds of formula (II), wherein A is $-N(CH_3)-CH_2-$, $-CH_2-N(CH_3)-$, R_4 or R_5 are hydroxy or R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:



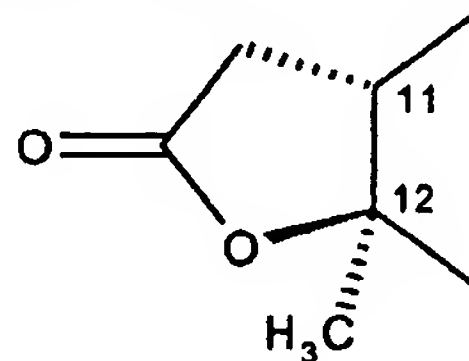
- 10 and R_6 is hydrogen are known compounds or they may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures described in EP 508699 and J.Chem. Res.Synop (1988 pages 152-153), USP 6262030.

- 15 Compounds of formula (II), wherein A is $-C(NOCH_2OCH_2CH_2OCH_3)-$, R_4 or R_5 are hydroxy or R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:

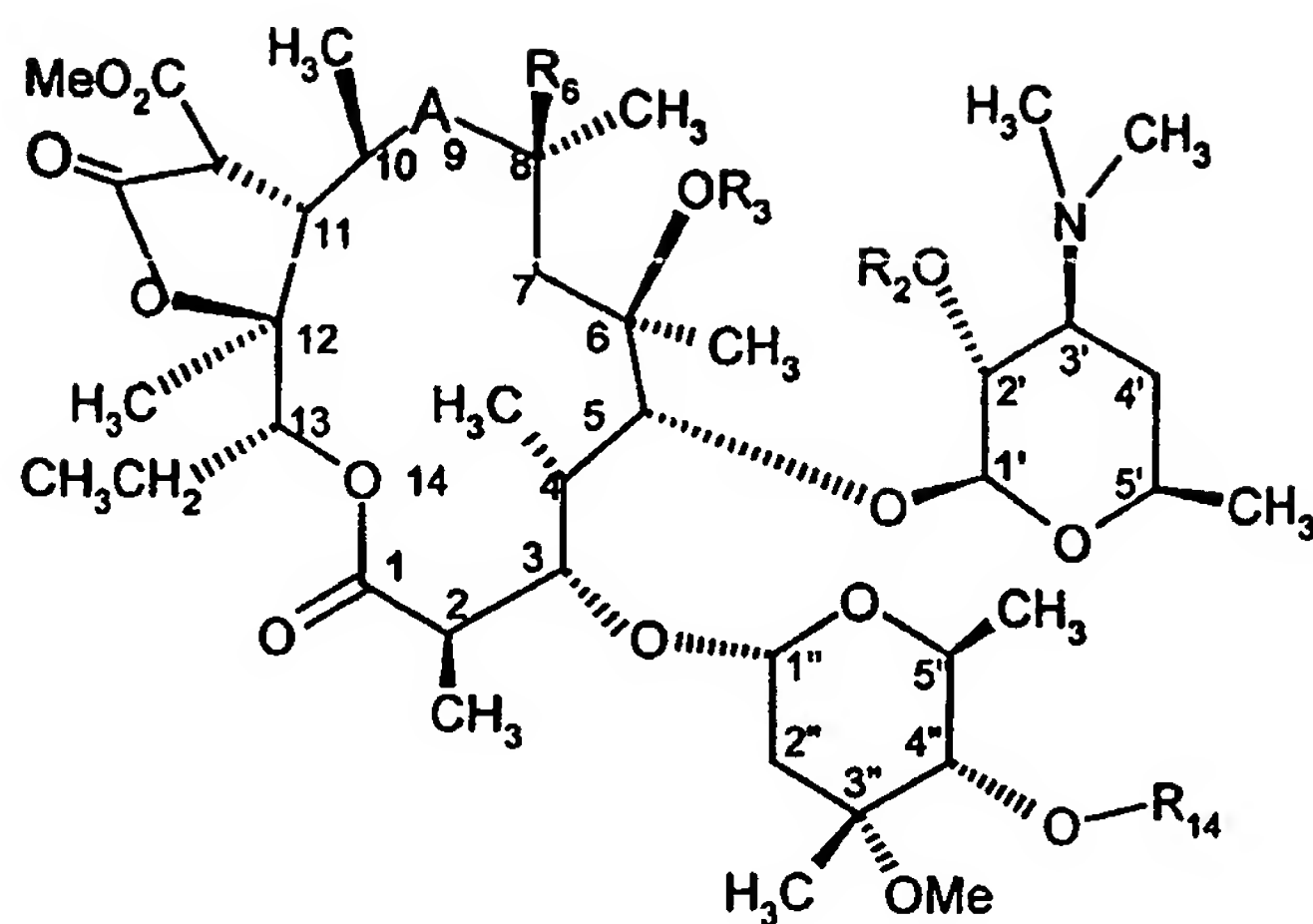


- 20 and R_6 is hydrogen, are known compounds or they may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures described in EP 284203.

Compounds of formula (II), wherein A is $C(O)-$, R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:



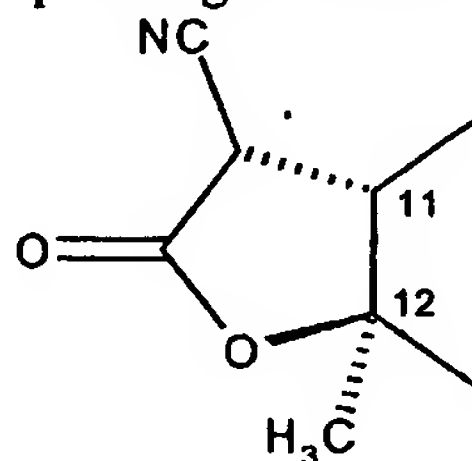
- 25 R_6 is hydrogen and R_3 is C_{1-4} alkyl may be prepared by decarboxylation of a compound of formula (X), wherein R_{14} is hydroxy protecting group, followed, if required by removal of the protecting group R_2 or R_{14} .



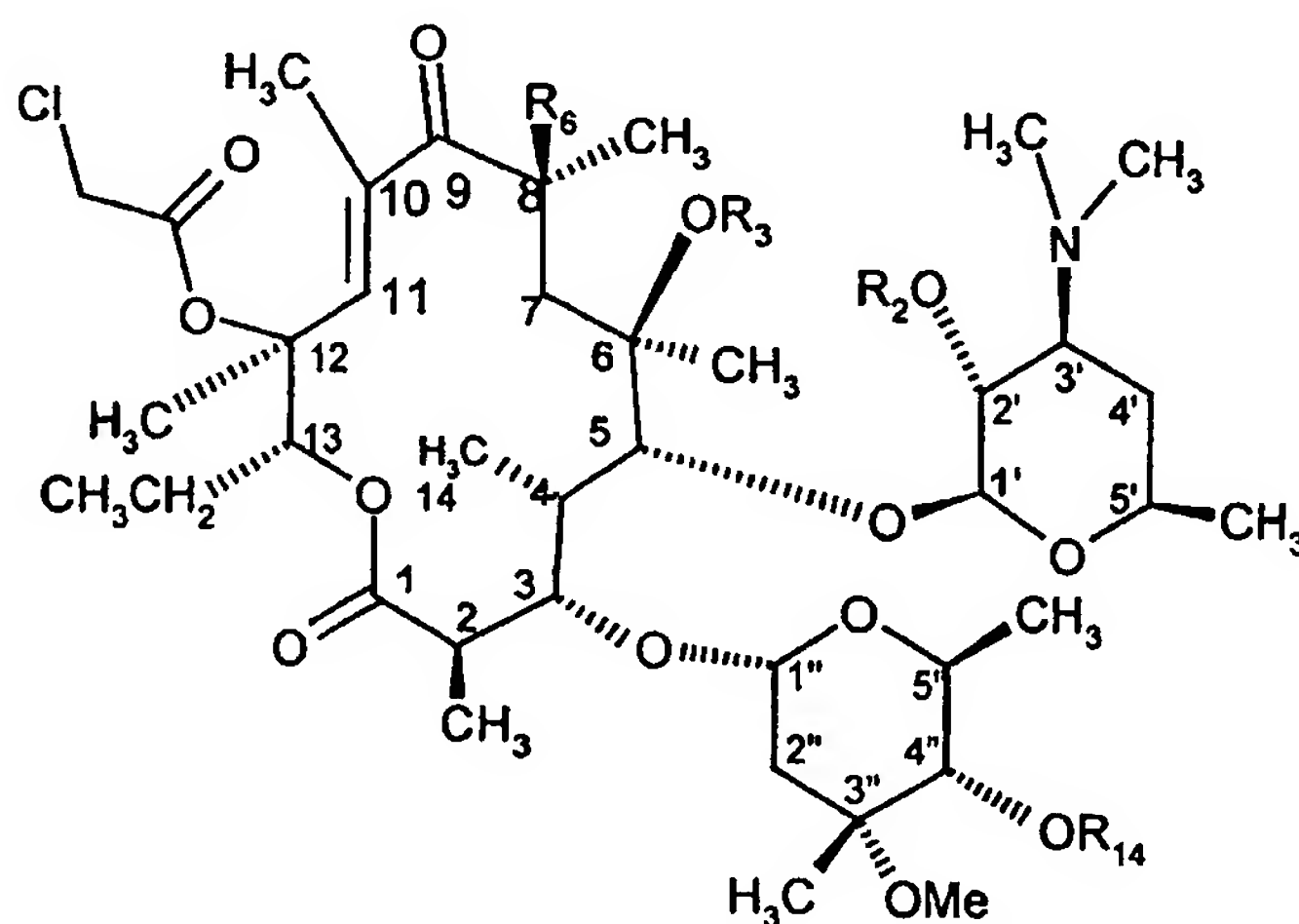
(X)

The decarboxylation may be carried out in the presence of a lithium salt such as lithium chloride, preferably in an organic solvent such as dimethylsulphoxide.

Compounds of formula (II), wherein A is $\text{C}(\text{O})-$, R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:



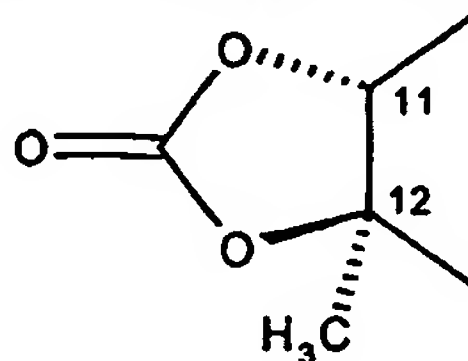
and R_3 is C_{1-4} alkyl may be prepared by cyclisation of chlorine derivatives (XI)



(XI)

with potassium cyanide and conveniently in the presence of a solvent such as N-N dimethylformamide.

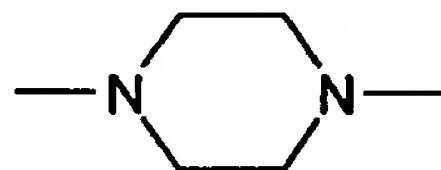
Compounds of formula (XIII) may be prepared by reacting a compound of formula (II) wherein R_{14} is hydroxy protecting group, R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:



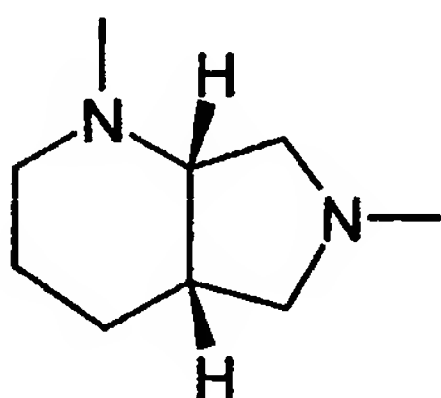
5 with a strong base such as 1,8 diazabicyclo [5.4.0]undec-7-ene.

Compounds of formula (XI) may be prepared by reaction of compounds of formula (XIII) with a suitable activated derivative of the acid HOCOCH_2Cl (XV). Thus, for example, the esterification may be carried out by reaction with anhydride $(\text{ClCH}_2\text{CO})_2\text{O}$ (XVI) in a suitable aprotic solvent such as a halohydrocarbon (e.g. dichloromethane) or N,N-dimethylformamide and in the presence of a tertiary base such as pyridine, dimethylaminopyridine or triethylamine and at a temperature within the range of 0° to 120°C .

Compounds of formula (III) wherein X is $-\text{U}(\text{CH}_2)_m\text{N}(\text{R}_{13})-$, in which U is $-\text{N}(\text{R}_{13})-$, $-\text{O}-$ or $-\text{S}-$ or X is a group selected from:



or

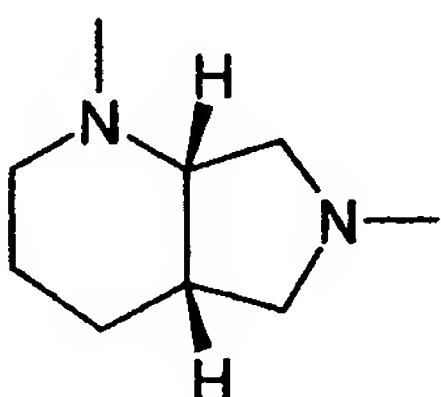


may be prepared by reaction of XR_7 (IV), wherein X has the meaning defined above with $\text{R}_{15}\text{OC}(\text{O})(\text{CH}_2)_n\text{L}$ (XV) wherein R_{15} is carboxyl protecting group and L is a suitable leaving group, followed by removal of R_{15} .

Compounds of formula (IV) wherein X is $-\text{U}(\text{CH}_2)_m\text{Z}$ in which Z is $-\text{N}(\text{R}_{13})-$, $-\text{O}-$, or $-\text{S}-$ or X is a group selected from:



or



may be prepared by reaction of a compound of formula R_7L (XVI), wherein L is a suitable leaving group such as chlorine, fluorine or bromine, with a compound of formula $U(CH_2)_mZ$ (XVII) in which Z is $-N(R_{13})-$, $-O-$, or $-S-$ or with piperazine or with 1H-pyrrolo[3,4-b]pyridine, octahydro.

5

Suitable hydroxy protecting reagents are those described by T.W. Greene and P.G.M Wuts in *Protective Groups in Organic Synthesis* 2nd ed., John Wiley & Son, Inc 1991, which is incorporated by reference. Examples of suitable hydroxy protecting reagents include acetic anhydride, benzoic anhydride or a trialkylsilyl chloride in a protic solvent. Examples of aprotic solvents are dichloromethane, N,N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran and the like. Suitable R_{15} carboxyl protecting group include t-butyloxy, allyl or benzyloxy.

Acid addition salts of the compounds of general formula (I) may prepared by various methods known to those skilled in those art. For example, an aqueous solution of an acid such as hydrochloric acid may be added to an aqueous suspension of a compound of formula (I) and the resulting mixture evaporated to dryness (lyophilised) to obtain the acid addition salt as a solid. Alternatively, a compound of formula (I) may be dissolved in a suitable solvent, for example an alcohol such as isopropanol, and the acid may be added in the same solvent or another suitable solvent. The resulting acid addition salt may then be precipitated directly, or by addition of a less polar solvent such as diisopropyl ether or hexane, and isolated by filtration.

In order that the invention may be more fully understood the following examples are given by way of illustration only.

In the Preparations and Examples, unless otherwise stated:

Proton Magnetic Resonance (1H -NMR) spectra were recorded on Bruker Avance DRX 300 and DRX 500 or Varian 500 MHz as solutions in chloroform d-1, unless otherwise stated. Chemical shifts are reported in ppm downfield (δ) from Me_4Si , used as internal standard, and are assigned as singlets (s), doublets (d), doublets of doublets (dd), triplets (t), quartets (q) or multiplets (m).

Carbon Magnetic Resonance (^{13}C -NMR) spectra were recorded on Bruker Avance DPX 75 and DRX 125 MHz as solutions in chloroform d-1, unless otherwise stated. Chemical shifts are reported in ppm downfield (δ) from Me_4Si , used as internal standard.

Mass spectra were acquired with a Hewlett Packard 1100 MSD system equipped with a binary pump (Agilent Technologies), operating in positive electrospray ionisation mode.

LC/MS data were obtained by using a HP 1100 LC system (Agilent Technologies) equipped with a Sedex Evaporative Light Scattering Detector model 75 (Sedere) coupled with a Platform LCZ Mass Spectrometer (Micromass) operating in positive electrospray ionisation mode. The chromatographic analysis conditions were: column Waters XTerra MS C18 (4.6 x 30mm, 2.5 μ m); flow rate 0.8mL/min; mobile phase: aqueous solution of NH_4OAc (10mM, pH 6.8) (A) and acetonitrile (B).

LC purifications were performed with a Waters 600 semi-preparative system equipped with a binary pumping system and a Jasco-UV detector. The chromatographic analysis conditions were:

column Supelcosil ABZ+Plus (10cm x 21.2mm, 5µm); flow rate 8mL/min; mobile phase: aqueous solution of NH₄OAc (10mM, pH 6.8) (A) and acetonitrile (B).

Column chromatography was carried out over silica gel 60 (230-400 mesh ASTM - Merck AG Darmstadt, Germany). The TLC monitoring was performed using Merck 60 F₂₅₄ as TLC plate.

5 Resin washings were carried out on Extract-clean Tube from Alltech.

Purifications of crude products were performed by SCX-cartridges from Varian.

The following abbreviations are used in the text: brine for saturated aqueous solution of sodium chloride, DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene, DCE for 1,2-dichloroethane, DCM for dichloromethane, NMP for 1-methyl-2-pyrrolidinone, DIPEA for N,N-diisopropylethylamine, DMAP for 4-dimethylaminopyridine, DMF for N,N-dimethylformamide, DMSO for dimethyl sulfoxide, EDC for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, Et₂O for diethyl ether, EtOAc for ethyl acetate, HATU for O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, MeOH for methanol, iPrOH for isopropanol; TEA for triethylamine, AcOH for acetic acid, THF for tetrahydrofuran, Ac₂O for acetic anhydride, TFA for trifluoroacetic acid and petrol refers to petroleum ether, boiling point 40-60 °C.

Solutions were dried over anhydrous sodium sulphate or potassium carbonate.

Intermediate 1

6-[(2-amino-ethyl)amino]-1-benzyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

To a solution of 1-Benzyl-6-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (300 mg) in 1-methyl-2-pyrrolidinone (6 mL) was added ethylenediamine (170 mg) under argon atmosphere. The mixture was heated at 120°C for 18 h and then at 145 °C for 4 h. The reaction mixture was cooled and poured into water (12 mL). The pH value was adjusted with acetic acid to 7.0-7.5. The reaction mixture was extracted with DCM (5x30 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica SPE-column (eluent: from DCM 100% to DCM/MeOH/NH₄OH 85/13/2) giving the title compound (80 mg).

¹³C-NMR (75 MHz, DMSO-d₆) δ: 176.1; 165.4; 149.0; 138.1; 134.2; 133.5; 131.9; 129.8; 129.5; 129.2; 127.1; 126.4; 118.9; 58.3; 42.8; 42.2.

Intermediate 2

7-[(2-amino-ethyl)amino]-1-benzyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

To a solution of 7-chloro-1-benzyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (1.0 g) in 1-methyl-2-pyrrolidinone (10 mL) was added ethylenediamine (0.95 g). The mixture was heated at 130°C for 10 h. The reaction mixture was cooled and poured into DCM (20 mL). The precipitate obtained was dispersed in MeOH, filtered to give the title compound (560mg).

¹H-NMR (300 MHz, DMSO-d₆) δ: 8.95 (s, 1H), 8.05 (d, 1H), 7.36 (m, 5H), 6.94 (d, 1H), 6.83 (m, 1H), 6.56 (s, 1H), 5.68 (s, 4H), 3.09 (m, 2H).

¹³C-NMR (75 MHz, DMSO-d₆) δ: 176.3, 166.5, 153.6, 148.6, 142.3, 135.5, 128.7, 127.8, 126.8, 126.7, 114.5, 94.9, 56.3, 45.8.

Intermediate 3

7-[(2-amino-ethyl)amino]-1-ethyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

To a solution of 7-chloro-1-ethyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (1,7 g) in 1-methyl-2-pyrrolidinone (20 mL) was added ethylenediamine (2,1 g). The mixture was heated at 130°C for 10 h. The reaction mixture was cooled and poured into DCM (20 mL). The precipitate obtained was dispersed in MeOH, filtered to give the title compound (830 mg).

5 MS; m/z (ES): 276 [MH]⁺.

¹H NMR (500 MHz, DMSO-d₆) δ: 8.80 (s, 1H), 8.03 (d, 1H), 7.17 (m, 1H), 6.95 (dd, 1H), 6.65 (s, 1H), 4.46 (q, 2H), 3.28 (q, 2H), 2.84 (q, 2H), 1.40 (t, 3H).

¹³C NMR (125 MHz, DMSO-d₆) δ: 176.1, 166.8, 153.7, 147.8, 141.8, 126.9, 115.0, 106.5, 95.9, 48.5, 44.6, 39.9, 14.2.

10

Intermediate 4

7-[(2-amino-ethyl)amino]-1-cyclopropyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

To a solution of 7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (2,0 g) in 1-methyl-2-pyrrolidinone (20 mL) was added ethylenediamine (2,3 g). The mixture was
15 heated at 130°C for 10 h. The reaction mixture was cooled and poured into DCM (20 mL). The precipitate obtained was dispersed in MeOH, filtered to give the title compound (910 mg).

¹H-NMR (500 MHz, DMSO-d₆) δ: 8.41 (s, 1H), 7.89 (d, 1H), 7.15 (m, 1H), 6.88 (s, 1H), 6.84 (dd, 1H), 6.56 (s, 1H), 3.56 (m, 1H), 3.16 (m, 2H), 2.75 (t, 2H), 1.17 (m, 2H), 1.01 (m,
20 2H).

¹³C-NMR (125 MHz, DMSO-d₆) δ: 176.1, 166.5, 153.6, 147.1, 143.7, 126.7, 114.3, 106.1, 44.5, 39.7, 35.3, 7.4.

Intermediate 5 and Intermediate 6

25 6-[(2-aminoethyl)amino]-7-chloro-1,4-dihydro-1-ethyl-4-oxo-quinoline-3-carboxylic acid (5) and 7-[(2-amino-ethyl)amino]-1,4-dihydro-1-ethyl-6-fluoro-4-oxo-quinoline-3-carboxylic acid (6)

7-Chloro-1,4-dihydro-1-ethyl-6-fluoro-4-oxo-quinoline-3-carboxylic acid (250mg) was dissolved in N,N-dimethylacetamide (5 mL) and ethylenediamine (223 mg) was added. The
30 reaction mixture was stirred for 10 h at 100°C, then left overnight at room temperature and heated again at 100°C for 7 h. Water (5mL) was added and the resulting precipitate was filtered, washed with water (5 mL) and dried to give a mixture containing the title compounds (120 mg).

MS; m/z (ES): 310.2 [MH]⁺ (intermediate 5), 294.2 [MH]⁺ (intermediate 6).

35

Intermediate 7 and Intermediate 8

6-[(2-amino-ethyl)amino]-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride (7) and 7-[(2-amino-ethyl)amino]-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid hydrochloride (8)

40 7-Chloro-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid (56.3 g) and ethylenediamine (36 g) were dissolved in N,N-dimethylacetamide (650 mL) at 100°C and stirred for 8.5 h at 115°C. Water (700 mL) was added to the reaction mixture cooled at room temperature. The reaction mixture was stirred at room temperature for 2 h, cooled at 0-5°C and stirred for 1 h. The precipitate obtained was filtered, washed with cold water, cold EtOH,

and dried at 110°C under reduced pressure for 1 h. The crude product was treated with HCl (6% aqueous solution) heating for 1 h in the presence of charcoal. After filtration, the solution was cooled to 35-40°C and a first precipitation happened. The precipitate was filtered, washed with water and dried at 110°C for 1 h. The title compound 7 (6.4 g) was obtained as hydrochloride salt. The mother liquors, after first precipitation, were cooled at room temperature and stirred overnight. The precipitate was filtered, washed with water and dried at 110°C for 1 h to give a mixture containing the title compounds 7 and 8 (14.18 g). Where necessary, the hydrochloride salts were converted to the corresponding free bases before use using standard conditions.

10 Intermediate 7

¹H-NMR (300 MHz, CF₃COOD) δ: 8.94 (s, 1H), 8.40 (s, 1H), 7.40 (s, 1H), 3.85 (m, 1H), 3.76 (m, 2H), 5.45 (m, 2H), 1.42 (m, 2H), 1.77 (m, 2H).

Intermediate 9

15 7-[(2-amino-butyl)amino]-1-cyclopropyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

To a solution of 7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (1.0 g) in 1-methyl-2-pyrrolidinone (10 mL) was added butylenediamine (1.7 g). The mixture was heated at 130°C for 16 h. The reaction mixture was cooled and poured into DCM (20 mL). The precipitate obtained was dispersed in MeOH and filtered to give the title compound (450 mg).

MS; (ES) m/z: 316.4 [MH]⁺.

Intermediate 10

25 6-[(2-amino-ethyl)amino]-3-carboxyquinoline-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo methyl ester.

A suspension of intermediate 7 (120 mg) in a solution of HCl in MeOH (3%, 30 mL) was sonicated in ultrasonic water bath at 60°C for 3 h and then at room temperature for 48 h. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (eluent: MeOH/DCM/NH₄OH 9/5/0.5. affording the title compound (80 mg).

30 ¹H-NMR (300 MHz, DMSO-d₆) δ: 8.37 (s, 1H), 8.04 (s, 1H), 7.36 (s, 1H), 5.77 (t, 1H), 3.37 (s, 3H, O-Me), 3.64 (m, 1H), 3.20 (q, 2H), 2.85 (t, 2H), 1.23 (m, 2H), 1.08 (m, 2H).

Intermediates 11 and 12

35 6-[(3-terbutoxycarbonylaminopropyl)amino]-7-chloro 1-cyclopropyl-1,4-dihydro -4-oxo-quinoline-3-carboxylic acid (11)
and 7-[(3-terbutoxycarbonylaminopropyl)amino]-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid (12)

40 In a sealed tube 1-N-(*tert*-butoxycarbonyl)-3-propanediamine (5 mL) was added to a solution of 7-chloro-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid (3 g) in DMSO (6 mL). The reaction mixture was stirred at 110°C for 15 h. The reaction mixture was allowed to cool at 50°C and was poured into ice, acetic acid was added to reach pH=5. A precipitate appeared and was separated by filtration and washed with ether to afford a mixture of 11 and 12 as a yellow solid (4.4 g). The mixture was purified by flash chromatography

(eluent: from EtOAc/cyclohexane/AcOH 80/15/5 to EtOAc/AcOH 90/10) affording the title compound 11 (801 mg) and the title compound 12 (780 mg).

Intermediate 13

5 6-[(3-aminopropyl)amino]-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A solution of intermediate 11 (100 mg) in 10% TFA/DCM (1 mL) was stirred at room temperature for 2 h. The solvent was partially evaporated under reduced pressure. For five times the residual was diluted in DCM (2 mL) and concentrated under reduced pressure. Final
10 solvent evaporation afforded the title compound (103 mg).

MS; m/z (ES): 336 [MH]⁺.

¹H-NMR (500MHZ, DMSO) δ: 8.56 (s, 1H), 8.22 (s, 1H), 7.35 (s, 1H), 6.54 (bt, 1H), 3.82 (m, 1H), 2.69 (t, 2H), 2.49 (m, 2H), 1.71 (m, 2H), 1.28 (m, 2H), 1.16 (m, 2H).

15 Intermediate 14

7-[(3-aminopropyl)amino]-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid

A solution of intermediate 12 (100 mg) in 10% TFA/DCM (1 mL) was stirred at room temperature for 2 h. The solvent was partially evaporated under reduced pressure. For five
20 times the residual was diluted in DCM (2 mL) and concentrated under reduced pressure. Final solvent evaporation afforded the title compound (103.4 mg).

MS; m/z (ES): 320 [MH]⁺.

¹H-NMR (500MHz, DMSO) δ: 8.56 (s, 1H), 7.78 (d, 1H), 7.31 (bm, 1H), 7.15 (d, 1H), 3.72 (m, 1H), 2.70 (t, 2H), 2.50 (m, 2H), 1.74 (m, 2H), 1.29 (m, 2H), 1.15 (m, 2H).

25 Intermediates 13 and 14 (mixture)

6-[(3-aminopropyl)amino]-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

and

30 7-[(3-aminopropyl)amino]-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid

To a solution of 7-chloro-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid (300 mg) in DMSO (1 mL), N-(*tert*-butoxycarbonyl)-3-propanediamine (0.37 mL) was added and the mixture was stirred at 110°C for 3 h. The reaction was diluted with DCM (3
35 mL), washed with water (3x50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was dissolved in HCOOH (5 mL) and stirred at room temperature for 12 h. The solvent was removed *in vacuo*, the crude product was washed several times with DCM (3x50 mL) and Et₂O (1x50 mL) and each time the solvent was evaporated under reduced pressure. The crude product obtained was purified by SCX
40 cartridge (eluent:DCM followed by MeOH and by NH₃ (0.2 N in MeOH)) affording the mixture of the title compounds (180 mg).

Intermediate 15 and Intermediate 16

6-[(2-tert-butoxycarbonylaminoethyl)amino]-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (15)

and 7-[(2-tert-butoxycarbonylaminoethyl)amino]-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid (16)

- 5 In a sealed tube N-(*tert*-butoxycarbonyl)ethylenediamine (5 mL) was added to a solution of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (3 g) in DMSO (6 mL). The reaction mixture was stirred at 110°C for 15 h. The reaction mixture was allowed to cool at 50°C and was poured into ice, acetic acid was added to reach pH=5. A precipitate appeared and was separated by filtration and washed with ether to afford a 40:60 mixture of
- 10 title compounds (4.4 g).

Intermediate 17 and Intermediate 18

6-[(2-tert-butoxycarbonylaminoethyl)amino]-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid amide (17)

- 15 and 7-[(2-tert-butoxycarbonylaminoethyl)amino]-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid amide (18)

To a solution of a 40:60 mixture of intermediates 15 and 16 (1 g) in anhydrous DCM (20 mL) and anhydrous THF (30 mL) at -5°C was added N-methylmorpholine (0.56 mL) followed by dropwise addition of isobutylchloroformate (0.64 mL). The reaction mixture was stirred for 1

20 h at room temperature and NH₄OH (33%, 20 mL) was added. The reaction mixture was concentrated under reduced pressure and an aqueous saturated solution of NH₄Cl (20 mL) was added. The obtained mixture was extracted with DCM (3x20 mL), the combined organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent DCM/MeOH from 99:1 to 95:5)

25 affording a 40:60 mixture of title compounds (528 mg).

Intermediate 19 and Intermediate 20

6-[(2-aminoethyl)amino]-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid amide-trifluoroacetic acid salt (19)

- 30 and 7-[(2-aminoethyl)amino]-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid amide-trifluoroacetic acid salt (20)

A 40:60 mixture of intermediates 17 and 18 (528 mg) was dissolved in a TFA solution (30 mL, 10% in DCM) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure to afford a 40:60 mixture of title

35 compounds (544 mg).

HPLC/MS analysis (mobile phase: A/B from 95/5 to 10/90 in 10 min, 10/90 for 5 min, mass range 100-800 amu): retention time: 6.19 min (321 [MH]⁺) and 5.63, (305 [MH]⁺).

Intermediate 21

- 40 2'-O-acetyl-8a-aza-8a-homoerythromycin A

To a solution of 8a-aza-8a-homoerythromycin A (2.0 g) in DCM (100 mL) NaHCO₃ (900 mg) and Ac₂O (0.280 mL) were added. The resulting solution was stirred overnight at room temperature. To this mixture brine (100 mL) and water (50 mL) were added. The organic

layer was separated, washed with brine (50 mL), dried over Na₂SO₄, filtered and evaporated under reduced pressure to afford the title compound (2.1 g).

MS; m/z (ES): 791.1 [MH]⁺.

5 **Intermediate 22**

2'-O-acetyl-4''-O-propenoyl-8a-aza-8a-homoerythromycin A

Intermediate 21 (290 mg) was dissolved in toluene (10 mL) and the solvent was evaporated. This operation was repeated 2 times. The residue was dissolved again in toluene (15 mL) and the solution was stirred under argon. TEA (0.470 mL) was added followed by 3-chloropropionyl chloride (0.101 mL) added in three portions over a period of 10 minutes. After 15 h TEA (0.235 mL) and 3-chloropropionyl chloride (0.050 mL) were added. Three h later TEA (0.170 mL) and 3-chloropropionyl chloride (0.025 mL) were added. After one h a saturated aqueous solution of NaHCO₃ (30 mL) was added and the aqueous phase was extracted with toluene (3x20 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound (261 mg).

Intermediate 23

4''-O-propenoyl-8a-aza-8a-homoerythromycin A

Intermediate 22 (225 mg) was dissolved in MeOH (30 mL) and stirred overnight. The solvent was evaporated under reduced pressure affording the title compound (221 mg).

MS; m/z (ES): 803.7 [MH]⁺.

Intermediate 24

2'-O-acetyl-6-O-methyl-8a-aza-8a-homoerythromycin A

To a solution of 6-OMethyl 8a-aza-8a-homoerythromycin A (1.62 g) in DCM (100 mL), NaHCO₃ (713 mg), and Ac₂O (0.230 mL) were added and stirred overnight. To this mixture brine (100 mL) and water (50 mL) were added. The organic layer was separated, washed with brine (50 mL), dried over Na₂SO₄, filtered and evaporated under reduced pressure affording the title compound (1.67 g).

MS; m/z (ES): 805.1 [MH]⁺.

Intermediate 25

2'-O-acetyl-4''-O-propenoyl-6-O-methyl-8a-aza-8a-homoerythromycin A

To a solution of intermediate 24 (1.80 g) in dry toluene (30 mL), under an argon atmosphere, was added TEA (2.90 mL) in one portion. To the reaction mixture was added 3-chloropropionyl chloride (0.63 mL) during several minutes. The reaction mixture was stirred for 2 h. Two more equivalents of TEA and one equivalent of 3-chloropropionyl chloride were added to the reaction solution and stirred for additional 2 h. The reaction was quenched via addition saturated NaHCO₃ (60 mL). The layers were separated and aqueous layer was extracted with toluene (3x30 mL). The combined toluene extracts were washed with brine (20 mL) dried over K₂CO₃, filtered and concentrated under reduced pressure affording the title compound (1.8 g).

MS; m/z (ES): 859 [MH]⁺.

Intermediate 26**4''-O-propenoyl-6-O-methyl-8a-aza-8a-homoerythromycin A**

The intermediate 25 (1.8 g) was dissolved in MeOH (100 mL) and the solution was stirred at room temperature for 24 h and then at 60 °C for 2 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (eluent MeOH/DCM/NH₄OH 5/90/0.5) affording the title compound (1.54 g).
MS; m/z (ES): 817.5 [MH]⁺.

Intermediate 27 and Intermediate 28

10 **6-O-ethyl-8a-aza-8a-homoerythromycin A (27) and 6-O-ethyl-9a-aza-9a-homoerythromycin A (28)**

To a suspension of 6-O-ethylerythromycin A 9(E)- and 9(Z)-oximes (3.76 g) in acetone and water (230 mL, mixture 1/1) at 0°C was added NaHCO₃ (5.69 g). A solution of *p*-toluenesulphonyl chloride (6.46 g) in acetone (55 mL) was added dropwise for 30 min and the resulting suspension was stirred for 15 h at room temperature. Acetone was evaporated under reduced pressure, DCM (100 mL) and H₂O (100 mL) were added. The pH of the resulting solution was adjusted to 9.5 with NaOH (2M). The organic layer was separated and washed with brine (50 mL), dried over K₂CO₃, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (eluent: ethyl-acetate/n-hexane/diethylamine 6/3/0.2) affording the title compound 27 (0.835 g) and the title compound 28 (1.38 g).
MS; m/z (ES): 777.5 [MH]⁺.

Intermediate 29

25 **2'-O-acetyl-6-O-ethyl-8a-aza-8a-homoerythromycin A**

To a solution of intermediate 27 (735 mg) in DCM (20 mL), NaHCO₃ (358 mg) and acetic anhydride (0.098 mL) were added stirring at room temperature for 20 h. Saturated solution of NaHCO₃ (20 mL) was added, water layer was washed with DCM (2x10 mL), organic layer was washed with brine (20 mL) dried over K₂CO₃, filtered and the filtrate was concentrated under reduced pressure, affording the title compound (661 mg).
MS; m/z (ES): 819.4 [MH]⁺.

Intermediate 30**2'-O-acetyl-6-O-ethyl-4''-O-propenoyl-8a-aza-8a-homoerythromycin A**

35 To a solution of intermediate 29 (149 mg) in dry toluene (5 mL) under nitrogen atmosphere TEA (0.229 mL) was added at room temperature, then 3-chloropropionyl chloride (0.05 mL) was added in three portions during 3 h. A saturated solution of NaHCO₃ (5 mL) was added, water layer was washed with toluene (2x5 mL), organic layer was washed with brine (10 mL), dried over K₂CO₃, filtered and the filtrate was concentrated under reduced pressure, affording the title compound (139 mg).
40 MS m/z (ES) 873.4 [MH]⁺.

Intermediate 31 and Intermediate 32

6-O-(2-propenyl)-8a-aza-8a-homoerythromycin A (31) and 6-O-(2-propenyl)-9a-aza-9a-homoerythromycin A (32)

To a suspension of 6-O-2-propenyl-erythromycin A 9(E)- and 9(Z)-oximes (4.25 g) in acetone/water 1/1 (250 mL) cooled to 0°C NaHCO₃ (6.34 g) was added. Then a solution of *p*-toluenesulphonyl chloride (7.19 g) in acetone (55 mL) was added dropwise in 30 min and the resulting suspension was stirred for 15 h allowing to rise to room temperature. Acetone was evaporated under reduced pressure and DCM (100 mL) and water (100 mL) were added. The pH of the solution was adjusted to 9.5 by addition of NaOH (2M). The organic layer was washed with brine (50 mL), dried over K₂CO₃ filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (eluent: EtOAc/n-hexane/Et₂NH 6/3/0.2) affording the title compound 31 (2.36 g) and the title compound 32 (0.97 g). MS; m/z (ES): 789.4 [MH]⁺.

Intermediate 33

6-O-propyl-8a-aza-8a-homoerythromycin A

A solution of intermediate 31 (2.3 g) in MeOH (40 mL) was acidified to pH 5-5.5 using HCl (1M). Then 10 % Pd/C (0.82 g) was added and the mixture was hydrogenated at 20 bar for 20 h. MeOH was evaporated under reduced pressure, then DCM (50 mL) and water (50 mL) were added. The pH was adjusted to 9.5 using NaOH (1M). The aqueous phase was extracted with DCM (10 mL) and the organic layer was washed with brine (50 mL), dried over K₂CO₃, filtered and evaporated under reduced pressure affording the title compound (1.84 g). MS; m/z (ES): 791.4 [MH]⁺.

Intermediate 34

2'-O-acetyl-6-O-propyl-8a-aza-8a-homoerythromycin A

To a solution of intermediate 33 (0.27 g) in DCM (10 mL), NaHCO₃ (131 mg) and acetic anhydride (0.039 mL) were added at room temperature. The resulting suspension was stirred at room temperature for 20 h. A saturated solution of NaHCO₃ (10 mL) was added, and the aqueous layer was extracted with DCM (2x10 mL). The organic phase was washed with brine (10 mL), dried over K₂CO₃, filtered, and evaporated under reduced pressure affording the title compound (0.25 g). MS; m/z (ES): 833.4 [MH]⁺.

Intermediate 35

2'-O-acetyl-4''-O-propenoyl-6-O-propyl-8a-aza-8a-homoerythromycin A

To a solution of intermediate 34 (149 mg) in dry toluene (5 mL) at room temperature, under nitrogen atmosphere TEA (0.229 mL) was added, then 3-chloropropionyl chloride (0.052 mL) was added in three portions every hour and then stirred for 2 h. A saturated solution of NaHCO₃ (5 mL) was added and the aqueous phase was washed with toluene (2x5 mL). The organic solution was washed with brine (10 mL), dried over K₂CO₃ filtered, and the filtrate was evaporated under reduced pressure affording the title compound (139 mg). MS; m/z (ES): 887.5 [MH]⁺.

Intermediate 36

2'-O-acetyl-11,12-carbonate-11,12-dideoxy-4''-O-(1H-1-imidazolylcarbonyl)-6-O-methyl-8a-aza-8a-homoerythromycin A

A solution of intermediate 24 (2.0 g) in dry DMF (20 mL) was cooled to 0°C in an ice-water bath, under argon atmosphere. Then 1,1'-carbonyldiimidazole (3.20 g) was added in one portion, followed by portionwise addition of NaH (60% oil suspension, 0.47 g). The resulting mixture was stirred under argon atmosphere at 0°C for 1 h. The reaction was quenched by dropwise addition of cold water (100 mL) during which a solid material precipitated. The solid was filtered and dried to give the title compound (2.02 g).

MS; m/z (ES): 925.9 [MH]⁺.

Intermediate 37

2'-O-acetyl-4''-O-trimethylsilyl-8a-aza-8a-homoerythromycin A

Intermediate 21 (1.0 g) was dissolved in DCM (10 mL) and cooled to 0-5°C, then pyridine (0.31 mL) and trimethylsilylchloride (0.33 mL) were added and the resulting mixture stirred for 2 h. The reaction mixture was washed with an aqueous solution of NaH₂PO₄ (30 mL), with water (30 mL) and brine (30 mL), and the solvent concentrated under reduced pressure affording the title compound (0.94 g).

MS; m/z (ES): 862 [MH]⁺.

Intermediate 38

11-O-[3-(3-quinolyl)-2-propenyl]-8a-aza-8a-homoerythromycin A

The intermediate 37 (0.9 g) and *cis*-propenylquinolyl *t*-butyl carbonate (0.630 g) were dissolved in toluene (18 mL) then the solvent was removed under reduced pressure. This operation was repeated twice, then the residue was dissolved in toluene (25 mL) and approximately 7 mL of solvent was removed *in vacuo*. The residual solution was transferred to a three-neck round-bottom flask and deoxygenated with argon. Tris(dibenzylideneacetone)dipalladium(0) (40 mg) and 1,4-Bis(diphenylphosphino)butane (37 mg) were added and the mixture heated at 80°C for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in MeOH (200 mL), formic acid was added adjusting the pH to 5 and the solution stirred overnight. The mixture was evaporated under reduced pressure to give a crude product that was purified by flash chromatography (eluent: CHCl₃/MeOH/NH₄OH 6/1/0.1) affording the title compound (260 mg).

MS; m/z (ES): 917 [MH]⁺.

Intermediate 39

2'-O-acetyl-11-O-[3-(3-quinolyl)-2-propenyl]-8a-aza-8a-homoerythromycin A

To a solution of intermediate 38 (0.30 g) NaHCO₃ (900 mg) and Ac₂O (0.280 mL) were added at room temperature. The resulting solution was stirred overnight. To this mixture brine (100 mL) and water (50 mL) were added. The organic layer was separated, washed with brine (50 mL), dried, filtered and evaporated under reduced pressure affording the title compound (0.30 g).

MS; m/z (ES): 958 [MH]⁺.

Intermediate 40

4''-O-propenoyl-11-O-[3-(3-quinolyl)-2-propenyl]-8a-aza-8a-homoerythromycin A

To a solution of intermediate 39 in dry toluene (5 mL), TEA (0.26 mL) and 3-chloropropionyl chloride (0.070 mL) were added. The reaction mixture was stirred for 0.5 h then quenched by addition of a saturated aqueous solution of sodium bicarbonate (15 mL). The aqueous phase
5 was extracted with toluene (10 mL). The combined toluene extracts were washed with brine (20 mL), dried over potassium carbonate filtered and concentrated under reduced pressure. The crude product was dissolved in MeOH (60 mL) and stirred at room temperature for 24 h. The solvent was evaporated to give the title compound (0.25 g).

MS; m/z (ES): 971 [MH]⁺.

Intermediate 41**2'-O-acetyl-6-O-methyl-9a-aza-9a-homoerythromycin A**

To a solution of 6-O-methyl-9a-aza-9a-homoerythromycin A (4.0 g) in DCM (60 mL) and acetone (10 mL) NaHCO₃ (2.2 g) and Ac₂O (1.5 mL) were added. The reaction mixture was
15 stirred for 1 h then DCM (75 mL) and water (75 mL) were added. The organic phase was separated, washed with brine (50 mL), dried over Na₂SO₄, filtered and evaporated under reduced pressure affording the title compound (4.02 g).

Intermediate 42**2'-O-acetyl-4''-O-propenyl-6-O-methyl-9a-aza-9a-homoerythromycin A**

To a solution of intermediate 41 (3.0 g) in dry toluene (30 mL), was added TEA (2.07 mL) under argon atmosphere. The reaction mixture was cooled to 15°C and 3-chloropropionyl chloride (0.71 mL), was added dropwise. The water bath was removed and the reaction mixture was stirred for 2 h, then TEA (1 mL) and 3-chloropropionyl chloride (0.48 mL) were
25 added and the reaction solution was stirred for additional 2 h. A saturated aqueous solution of NaHCO₃ (60 mL), and EtOAc (30 mL), were added and the aqueous phase was extracted with EtOAc (2x 30 mL). The combined organic extracts were dried over K₂CO₃, filtered and concentrated under reduced pressure affording of the title compound (3.17 g).

MS; m/z (ES): 859 [MH]⁺.

Intermediate 43**4''-O-propenoyl 6-O-methyl-9a-aza-9a-homoerythromycin A**

Intermediate 42 (2.9 g), was dissolved in MeOH (100 mL) and the solution was stirred at room temperature for 24 h then at 60°C for 2 h. The solvent was evaporated and the residue
35 was purified by flash chromatography (eluent: MeOH/DCM/NH₄OH 5/90/0.5) affording the title compound (1.8 g).

MS; m/z (ES): 817 [MH]⁺.

Intermediate 44**2'-O-acetyl-6-O-ethyl-9a-aza-9a-homoerythromycin A**

To a solution of intermediate 28 (1.33 g) in DCM (30 mL) at room temperature, NaHCO₃ (650 mg) and Ac₂O (0.178 mL) were added. The resulting suspension was stirred at room temperature for 20 h. A saturated aqueous solution of NaHCO₃ (20 mL) was added, the aqueous phase was extracted with DCM (2x20 mL), and the combined organic solution was

washed with brine (20 mL), dried over K_2CO_3 , filtered and evaporated under reduced pressure affording the title compound (1.29 g).

MS; m/z (ES): 819.4 $[MH]^+$.

5 **Intermediate 45**

2'-O-acetyl-4''-O-propenoyl-6-O-ethyl-8a-aza-8a-homoerythromycin A

To a solution of intermediate 44 (0.21 g) in dry toluene (5 mL) at room temperature, under nitrogen atmosphere, TEA (0.321 mL), was added. Then 3-chloropropionyl chloride (0.073 mL) was added in three portions over three hour and then stirred for 2 h. A saturated solution of $NaHCO_3$ (5 mL) was added and the aqueous phase was washed with toluene (2x10 mL). The organic solution was washed with brine (10 mL), dried over K_2CO_3 , filtered, and evaporated under reduced pressure affording the title compound (0.20 g).

MS; m/z (ES): 873.4 $[MH]^+$.

15 **Intermediate 46**

6-O-propyl-9a-aza-9a-homoerythromycin A

To a solution of intermediate 32 (1.27 g) in MeOH (40 mL), an aqueous solution of HCl (1M) was added until pH = 5-5.5 was obtained. To the solution 10% Pd/C (0.45 g) was added and the mixture was hydrogenated at 15 bars for 20 h. The solution was concentrated under reduced pressure and DCM (50 mL) and water (50 mL) were added. The pH of the resulting mixture was adjusted to 9.5 by addition of NaOH (1M). The aqueous phase was washed with DCM (30 mL), and the organic solutions were combined and washed with brine (50 mL), dried over K_2CO_3 and evaporated under reduced pressure affording the title compound (0.97 g).

25 MS; m/z (ES): 791.4 $[MH]^+$.

Intermediate 47

2'-O-acetyl-6-O-propyl-9a-aza-9a-homoerythromycin A

To a solution of intermediate 46 (0.97 mg) in DCM (50 mL) at room temperature were added $NaHCO_3$ (0.46 g) and Ac_2O (0.139 mL). The resulting suspension was stirred at room temperature for 20 h. An aqueous saturated solution of $NaHCO_3$ (50 mL) was added, and extracted with DCM (2x20 mL). The combined organic solution was washed with brine (40 mL), dried over K_2CO_3 , filtered and evaporated under reduced pressure affording the title compound (0.95 g).

35 MS; m/z (ES): 833.4 $[MH]^+$.

Intermediate 48

2'-O-acetyl-4''-O-propenoyl-6-O-propyl-8a-aza-8a-homoerythromycin A

To a solution of intermediate 47 (0.95 g) in dry toluene (25 mL) at room temperature, under nitrogen atmosphere triethylamine (0.958 mL) was added, then 3-chloropropionyl chloride (0.218 mL) was added in three portions every hour and then stirred for 2 h. An aqueous saturated solution of $NaHCO_3$ (25 mL) was added and the aqueous phase was washed with toluene (2x25 mL). The organic phase was washed with brine (50 mL), dried over K_2CO_3 , filtered, and evaporated under reduced pressure affording the title compound (0.92 g).

MS; m/z (ES): 887.4 [MH]⁺.

Intermediate 49

2'-O-acetyl-11,12-carbonate-11,12-dideoxy-4''-O-propenoyl-azithromycin

- 5 A solution of intermediate 2'-O-acetyl-11,12-carbonate-11,12-dideoxy-azithromycin (10.9 g) in toluene (300 mL) was stirred at room temperature under argon atmosphere. To this solution TEA (12.66 mL) and 3-chloro-propionyl chloride (1.94 mL) were added in two portions over a period of 10 minutes. After 20 minutes the solution was diluted with a saturated aqueous solution of NaHCO₃ (300 mL) and extracted with toluene (4x80 mL). The collected organic
- 10 phase was dried, filtered and concentrated under reduced pressure affording the title compound (11.0 g).

MS; m/z (ES): 872 [MH]⁺.

Intermediate 50

11,12-carbonate-11,12-dideoxy-4''-O-propenoyl azithromycin

- 15 A solution of intermediate 49 (11.0 g) in MeOH (200 mL) was stirred at room temperature for 48 h. The solvent was evaporated under reduced pressure affording the title compound (9.81 g).

MS; m/z (ES): 829.1 [MH]⁺.

- 20 ¹H-NMR (500 MHz, δ): 6.45 (d, 1H), 6.17 (dd, 1H), 5.87 (d, 1H), 5.11 (d, 1H), 4.88 (dd, 1H), 4.77 (d, 1H), 4.53 (d, 1H), 4.47-4.40 (m, 3H), 3.72 (m, 1H), 3.60 (d, 1H), 3.33 (s, 3H), 3.25 (dd, 1H), 2.87-2.85 (m, 2H), 2.58 (m, 1H), 2.44-2.38 (m, 2H), 2.32 (s, 6H), 2.21 (s, 3H), 2.06 (m, 1H), 2.00 (m, 1H), 1.92 (m, 1H), 1.84 (m, 1H), 1.70-1.56 (m, 4H), 1.45 (s, 3H), 1.40 (dd, 1H), 1.29 (s, 3H), 1.25 (m, 1H), 1.22 (d, 3H), 1.18 (d, 6H), 1.12 (s, 3H), 1.08-1.06 (2d, 6H),
- 25 0.93 (m, 6H).

Intermediate 51

4''-O-propenoyl-azithromycin

- 30 To a solution of intermediate 50 (1.3 g) in acetonitrile (50 mL), a saturated aqueous solution of potassium carbonate (30 mL) was added at room temperature. The resulting mixture was heated to 70°C for 8 h. The mixture was then diluted with water (100 mL), extracted with EtOAc (4x30 mL). The collected organic phase was dried, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent: DCM/MeOH/NH₃ 90/9/0.5) affording the title compound (530 mg).

- 35 MS; m/z (ES): 804 [MH]⁺.

Intermediate 52

2'-O-acetyl-4''-O-imidazolylcarbonyl azithromycin

- 40 To a solution of 2'-O-acetyl azithromycin (0.8 g) in dry toluene (30 mL) under an argon atmosphere K₂CO₃ (420 m), and 1,1'-carbonyldiimidazole (0.170g) were added. The reaction mixture was stirred at RT for 20 h, and at 40 °C for additional 5 h. A saturated solution of NaHCO₃ (30mL) was added and the aqueous phase was washed with toluene (2x30 mL). The combined organic solution was dried over K₂CO₃ and concentrated under reduced pressure affording the title compound (0.82 g)

MS; m/z (ES): 885 [MH]⁺.

Intermediate 53

2'-O-acetyl-6-O-methyl-azithromycin

5 To a solution of 6-O-methyl-azithromycin (205 mg) in DCM (10 mL), NaHCO₃ (112.8 mg) and Ac₂O (0.030 mL) were added. The mixture was stirred at room temperature for 20 h, then brine (20 mL) was added. The solution was extracted with DCM and the organic phase was dried. The solvent was concentrated under reduced pressure affording the title compound (220 mg).

10 MS; m/z (ES): 805 [MH]⁺.

Intermediate 54

4"-O-propenoyl-6-O-methyl-azithromycin

15 A solution of intermediate 53 (215 mg) in DCM (10 mL) was stirred under argon atmosphere for 10 min. TEA (0.222 mL) and 3-chloro-propionylchloride (0.051 mL) were added in two portions. 15 min later again TEA (0.111 mL) and 3-chloro-propionylchloride (0.026 mL) were added. 12 h later TEA (0.111 mL) and 3-chloro-propionylchloride (0.026 mL) were added. The reaction mixture was stirred at room temperature for 2 h. A saturated aqueous solution of NaHCO₃ (20 mL) was added. The layers were separated and the organic phase
20 was dried. The solvent was concentrated under reduced pressure and the residue (240 mg) was dissolved in MeOH (20 mL) and stirred at room temperature for 14 h. The solvent was concentrated under reduced pressure affording the title compound (220 mg).

MS; m/z (ES): 817.6 [MH]⁺.

Intermediate 55

2'-O-acetyl-11,12-(aminocarbonyloxy)-11,12-dideoxy-6-O-methyl-erythromycin A

To a solution of 11,12-(aminocarbonyloxy)-11,12-dideoxy-6-O-methyl-erythromycin A in DCM (50 mL) was added NaHCO₃ (478 mg) at room temperature. To this solution Ac₂O (0.153 mL) was added and stirred overnight. To this mixture brine (50 mL) and water (20
30 mL) were added. The organic layer was separated, washed with brine (20 mL), dried, filtered and evaporated under reduced pressure, affording the title compound (1.2 g).

MS; m/z (ES): 816.2 [MH]⁺.

Intermediate 56

2'-O-acetyl-11,12-(aminocarbonyloxy)-11,12-dideoxy-6-O-methyl-4"-O-propenoyl-erythromycin A

Intermediate 55 was dissolved in toluene (50 mL) and the solvent was evaporated. This was performed 2 times. After that the residue was again dissolved in toluene (45 mL) and stirred under argon. To this solution TEA (1.8 mL) and 3-chloropropionylchloride (0.40 mL) (in 3
40 portions in a period of 20 minutes) were added. 20 min later a saturated aqueous solution of NaHCO₃ (50 mL) was added. The aqueous solution was extracted with toluene (3x50 mL), the combined organic solution dried over K₂CO₃ and the solvent removed under reduced pressure affording the title compound (1.04 g).

MS; m/z (ES): 870.1 [MH]⁺.

Intermediate 57**11,12-(aminocarbonyloxy)-11,12-dideoxy-6-O-methyl-4''-O-propenoyl-erythromycin A**

A solution of intermediate 56 in MeOH (30 mL) was stirred at room temperature overnight.

5 The solvent was concentrated under reduced pressure affording the title compound (1.2 g).

MS; m/z (ES): 828.1 [MH]⁺.

¹H-NMR (500 MHz) δ: 6.44 (d, 1H), 6.13 (dd, 1H), 5.89 (d, 1H), 5.11 (dd, 1H), 4.98 (d, 1H), 4.75 (d, 1H), 4.60 (d, 1H), 4.36 (m, 1H), 3.80 (d, 1H), 3.73 (m, 1H), 3.70 (s, 1H), 3.62 (d, 1H), 3.34 (m, 1H), 3.32 (s, 3H), 3.22 (m, 1H), 2.95 (s, 3H).

10 ¹³C-NMR (125 MHz) δ: 218.4; 176.9; 166.2; 158.8; 132.0; 128.4; 102.5; 96.2; 84.3; 80.7; 79.1; 78.8; 77.8; 76.1; 73.2; 71.4; 68.2; 65.83; 63.6; 58.2; 58.2; 50.6; 49.9; 45.6; 45.5; 41.1; 40.7; 40.0; 39.9; 37.8; 35.5; 22.4; 21.9; 21.4; 20.1; 18.6; 18.5; 16.1; 14.1; 13.6; 10.8; 9.5.

Intermediate 58

15 **2'-O-acetyl-11,12-dideoxy-6-O-methyl-11,12-(methylaminocarbonyloxy)-erythromycin**

A

11,12-dideoxy-6-O-methyl-11,12-(methylaminocarbonyloxy)-erythromycin A (0.87 g) was dissolved in DCM (20 mL) and acetone (3 mL). Solid NaHCO₃ (0.6 g) and Ac₂O (0.6 mL) were added and the reaction mixture was stirred for 1 h, then DCM (50 mL) and water (50 mL) were added. The organic phase was separated, washed with brine (20 mL), dried over K₂CO₃, filtered and concentrated under reduced pressure, affording the title compound (0.875 g).

MS; m/z (ES): 829.2 [MH]⁺.

25 **Intermediate 59**

11,12-dideoxy-6-O-methyl-11,12-(methylaminocarbonyloxy)-4''-O-propenoyl-erythromycin A

To a solution of intermediate 58 (0.85 g) in dry toluene (10 mL) under argon atmosphere, TEA (0.85 mL) and 3-chloropropionyl chloride (0.196 mL, in 2 portions over a period of 20 minutes) were added and the reaction mixture was stirred for 1 h. Then a saturated solution of NaHCO₃ (30 mL) was added and the mixture was extracted with toluene (2x60 mL). The combined organic solution was washed with brine (20 mL) dried over K₂CO₃, filtered and concentrated under reduced pressure. The residue was dissolved in MeOH (70 mL) and heated at 60°C for 4 h then allowed to stand at room temperature for 24 h. The solvent was

30 concentrated under reduced pressure affording the title compound (620 mg).

MS; m/z (ES): 841 [MH]⁺.

¹H-NMR (300 MHz) δ: 6.44 (d, 1H), 6.13 (dd, 1H), 5.90 (d, 1H), 4.97 (m, 2H), 4.75 (d, 1H), 4.60 (d, 1H), 4.36 (m, 1H), 3.77 (m, 3H), 3.64 (d, 1H), 3.55 (s, 1H).

40 **Intermediate 60**

2'-O,4''-O-diacetyl-11-deoxy-10,11-didehydro-12-O-(1H-1-imidazolcarbonyl)-6-O-methyl-erythromycin A

A solution of 2'-O,4''-O-diacetyl-6-O-methyl-erythromycin A (4.0 g) was dissolved in DMF (20 mL) at 0°C under argon atmosphere and N,N-carboxyldiimidazole (1.6 g) was added.

Then NaH (1.2 g, 50% suspension in oil) was added portionwise in a period of 30 min. The reaction mixture was stirred for 4 h then H₂O (60 mL) was added. The precipitate was filtered, washed with water and dried, affording the title compound (4.1 g).

5 Intermediate 61

2'-O,4"-O-diacetyl-11,12-dideoxy-11,12-(ethylaminocarbonyloxy)-6-O-methyl-erythromycin A

Intermediate 60 (3.5 g) was dissolved in CH₃CN (35 mL) and H₂O (4 mL) at room temperature and the reaction solution was cooled to 0°C in an ice-water bath, under an argon atmosphere. EtNH₂ (1.7 g) was added and the reaction mixture was stirred for 20 h. Water (50 mL) was added and the precipitate was filtered, washed with water and dried, affording the title compound (2.6 g).

Intermediate 62

15 11,12-dideoxy-11,12-(ethylaminocarbonyloxy)-6-O-methyl-erythromycin A

Intermediate 61 (2.5 g) was dissolved in MeOH (140 mL) and a saturated aqueous solution of K₂CO₃ (10 mL) was added and the reaction mixture was stirred at 75°C for 4 h and at room temperature overnight. The volume of the solution was halved under reduced pressure and EtOAc (100 mL) and water (50 mL) were added to the residue. The organic layer was separated, dried and evaporated to afford the title compound (2.4 g).

Intermediate 63

2'-O-acetyl-11,12-dideoxy-11,12-(ethylaminocarbonyloxy)-6-O-methyl-erythromycin A

Intermediate 62 (1.5 g) was dissolved in DCM (40 mL) and acetone (5 mL). Solid NaHCO₃ (1.2 g) and Ac₂O (0.8 mL) were added and the mixture was stirred for 1 h. Then DCM (60 mL) and water (60 mL) were added and the organic phase was separated, washed with brine (20 mL), dried and evaporated affording the title compound (1.5 g).

MS; m/z (ES): 843.2 [MH]⁺.

30 Intermediate 64

11,12-dideoxy-11,12-(ethylaminocarbonyloxy)-6-O-methyl-4"-O-propenoyl-erythromycin A

To a solution of intermediate 63 (1.45 g) in dry toluene (17 mL) under argon atmosphere TEA (1.42 mL) and 3-chloropropionyl chloride (0.49 mL, in 3 portions in a period of 20 minutes) were added. The reaction mixture was stirred for 1 h, then a saturated solution of NaHCO₃ (50 mL) was added and the aqueous phase was extracted with toluene (2x70 mL). The combined organic solution was washed with brine (20 mL), dried over K₂CO₃, filtered and concentrated under reduced pressure. The residue was dissolved in MeOH (100 mL) and heated at 60°C for 4 h then at room temperature for 24 h. The solvent was evaporated and the crude product was purified by flash chromatography (eluent: MeOH/DCM/NH₄OH 5/90/0.5) affording the title compound (1.4 g).

MS; m/z (ES): 855 [MH]⁺.

¹H-NMR (500 MHz) δ: 6.44 (d, 1H), 6.13 (dd, 1H), 5.89 (d, 1H), 4.99 (m, 2H), 4.75 (d, 1H), 4.60 (d, 1H), 4.38 (m, 1H), 3.77-3.55 (m, 6H), 3.32 (s, 3H), 3.20 (m, 1H), 3.06 (m, 1H), 3.05

(s, 3H), 2.95 (m, 1H), 2.61-2.52 (m, 2H), 2.43 (d, 1H), 2.31 (s, 6H), 1.98-1.89 (m, 2H), 1.73 (d, 1H), 1.68-1.64 (m, 2H), 1.55-1.49 (m, 1H), 1.39 (s, 3H), (d, 1H), 1.38 (s, 3H), 1.25-1.12 (m), 1.02 (d, 3H), 0.84 (t, 3H).

¹³C-NMR (125 MHz) δ : 216.1; 176.3; 165.8; 157.2; 131.5; 128.0; 102.2; 96.0; 82.6; 79.8; 78.7; 77.6; 76.1; 75.9; 73.7; 71.1; 67.9; 65.3; 63.2; 60.0; 50.5; 49.5; 45.6; 45.1; 40.3; 38.9; 38.8; 38.7; 38.6; 35.2; 28.8; 21.9, 21.7; 21.0; 20.1; 18.9, 18.6, 18.3; 15.9; 14.2; 14.1; 12.7; 10.3; 9.1.

Intermediate 65

10 2'-O-acetyl-11,12-dideoxy-11,12-[(N-(4-phenylbutyl)amino)carbonyloxy]-6-O-methyl-erythromycin A

To a solution of 11,12-dideoxy-11,12-[(N-(4-phenylbutyl)amino)carbonyloxy]-6-O-methyl-erythromycin A (0.550 g) in DCM (17 mL), acetic anhydride (0.101 mL) and NaHCO₃ (0.140 g) were added. The mixture was stirred at room temperature for 24 h then a saturated solution of NaHCO₃ (25 mL) was added. The organic phase was separated, washed with brine (15 mL) and water (15 mL) dried and evaporated affording the title compound (0.530 g).
MS; m/z (ES): 904 [MH]⁺.

Intermediate 66

20 2'-O-acetyl-11,12-dideoxy-11,12-[(N-(4-phenylbutyl)amino)carbonyloxy]-6-O-methyl-4''-O-propenoyl-erythromycin A

To a solution of intermediate 65 (0.500 g) in dry toluene (8 mL) under argon atmosphere, TEA (0.440 mL) and 3-chloropropionyl chloride (0.116 mL) were added in two portions. The reaction mixture was stirred at room temperature for 0.5 h. A saturated solution of NaHCO₃ (25 mL) was added, and the aqueous phase was extracted with toluene (2x10 mL). The combined organic extracts were washed with brine (25 mL), dried over K₂CO₃ filtered and concentrated under reduced pressure affording the title compound (0.450 g).

Intermediate 67

30 11,12-dideoxy-11,12-[(N-(4-phenylbutyl)amino)carbonyloxy]-6-O-methyl-4''-O-propenoyl-erythromycin A

Intermediate 66 (0.450 g) was stirred in MeOH (110 mL) at room temperature for 48 h. Evaporation under reduced pressure gave the title compound (0.420 g).
MS; m/z (ES): 959 [MH]⁺.

Intermediate 68

40 2'-O-acetyl-6-O-methyl-4''-O-propenoyl-erythromycin A

To a solution of 2'-O-acetyl-6-O-methyl-erythromycin A (1.1 g) in DCM (20 mL) pyridine (1.7 mL) and acryloylchloride (1.1 mL) were added at 0°C. After 2 h a further addition of pyridine (1.7 mL) and of acryloylchloride (1.1 mL) was performed. The reaction mixture was quenched with a saturated solution of NH₄Cl (10 mL) and extracted with DCM (3x20 mL). The organic phase was washed with a saturated solution of NaHCO₃ (10 mL), water (10 mL), dried over Na₂SO₄, filtered and evaporated under reduced pressure. The crude product was

purified by flash-chromatography (DCM/MeOH/NH₃ 95/5/0.5) affording the title compound (470 mg).

Intermediate 69

5 6-O-methyl-4''-O-propenoyl-erythromycin A

Intermediate 68 (1.82 g, mmol) was dissolved in MeOH (100 mL) and stirred at 60°C for 4 h, then at room temperature for 16 h. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (eluent: MeOH/DCM/NH₄OH 5/90/0) affording the title compound (1.4 g).

10 MS; m/z (ES): 802 [MH]⁺.

¹H-NMR (500 MHz) δ: 6.44 (d, 1H), 6.13 (dd, 1H), 5.89 (d, 1H), 5.07 (d, 1H), 5.00 (d, 1H), 4.75 (d, 1H), 4.60 (d, 1H), 4.38 (m, 1H), 3.97 (s, 1H), 3.80-3.73 (m, 2H), 3.66 (d, 1H), 3.46 (s, 1H), 3.32 (s, 3H), 3.21-3.18 (m, 2H), 3.04 (s, 3 H), 3.00 (m, 1H), 2.92 (m, 1H), 2.56 (m, 2H), 2.43 (d, 1H), 2.31 (s, 6H).

15 ¹³C-NMR (75 MHz) δ: 221.0; 175.7; 165.8; 131.5; 128.0; 102.1; 96.0; 80.5, 78.8, 78.3; 78.0; 76.6; 74.3, 72.7; 71.1; 69.1; 67.8; 65.3; 63.2; 50.7; 49.5; 45.3; 44.9; 40.3; 39.2; 38.8; 37.2; 35.2; 28.9; 21.7, 21.1; 19.7, 18.3, 18.0, 15.9; 12.3; 10.6; 9.1.

Intermediate 70

20 2'-O-acetyl-4''-O-iodoethanoyl-6-O-methyl-erythromycin A

To a solution of 2'-O-acetyl-6-O-methyl-erythromycin A (600 mg) in anhydrous DCM (40 mL), pyridine (0.18 mL) and chloroacetyl chloride (0.06 mL) were added and the reaction mixture was stirred at room temperature for 15 min. A second addition of pyridine (0.18 mL) and chloroacetyl chloride (0.06 mL) was performed. After further 15 min a third addition of pyridine (0.18 mL) and chloroacetyl chloride (0.06 mL) was performed followed by a fourth addition of pyridine (0.18 mL) and chloroacetyl chloride (0.06 mL) after further 30 min. The reaction mixture was further stirred for 1 h, then brine was added (20 mL). The aqueous phase was extracted with DCM (3x20 mL) and the combined organic layers were washed with a saturated aqueous solution of NaHCO₃ (20 mL). The organic phase was dried, filtered and concentrated under reduced pressure. To the crude product dissolved in acetone (4 mL), a solution of sodium iodide (570 mg) in acetone (6 mL), was added. The reaction mixture was then stirred at room temperature for 1 h, filtered and the filtrate concentrated under reduced pressure. The crude product was dissolved in EtOAc (10 mL), water (10 mL) was added and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic layers were washed with a saturated aqueous solution of Na₂S₂O₅ (10 mL), dried, filtered and concentrated under reduced pressure affording the title compound (546 mg).

35 ¹H-NMR (500MHz) δ: 5.00 (d, 1H), 4.81 (bt, 1H), 4.74 (d, 1H), 4.66 (d, 1H), 4.34 (m, 1H), 3.76 (m, 1H), 3.71 (d+d, 2H), 3.37 (s, 3H), 2.40 (d, 1H), 2.10 (s, 3H), 1.67 (m, 2H), 1.32 (m, 1H), 1.24 (d, 3H), 1.13 (d, 3H).

Intermediate 71

6-O-propyl-erythromycin A

To a solution of 6-O-(2-propenyl)-erythromycin A (2.5 g) in MeOH (60 mL), Pd/C (10%, 0.85 g) was added and the mixture was hydrogenated at room temperature at 15 bar for 20 h.

The catalyst was filtered and washed with MeOH and the solvent was evaporated under reduced pressure. DCM (50 mL) and water (50 mL) were added and the pH was adjusted to 9.5 by addition of NaOH (1M). The organic phase was dried over K₂CO₃, filtered and evaporated under reduced pressure affording the title compound (2.27 g).

5 MS; m/z (ES): 776.6 [MH]⁺.

Intermediate 72

2'-O-acetyl-6-O-propyl-erythromycin A

10 To a solution of intermediate 71 (1.0 g) in DCM (30 mL), NaHCO₃ (0.487 g) and Ac₂O (0.134 mL) were added at room temperature. The solution was stirred for 24 h then water (20 mL) was added and the pH was adjusted to 9.5 by addition of NaOH (1M), organic layer was dried over K₂CO₃, filtered and evaporated under reduced pressure affording the title compound (1.0 g).

MS; m/z (ES): 818.6 [MH]⁺.

15

Intermediate 73

2'-O-acetyl-4''-O-propenoyl-6-O-propyl-erythromycin A

20 Intermediate 72 (1.0 g) was dissolved in dry toluene (40 mL) under N₂, TEA (0.513 mL) and 3-chloropropionyl chloride (0.116 mL) were added and the solution was stirred for 30 minutes. Additional amounts of TEA (0.513 mL) and 3-chloropropionyl chloride (0.116 mL) were added after a 1 h and after 2 h. The reaction mixture was quenched by addition of a saturated aqueous solution of NaHCO₃ (30 mL), the organic layer was washed with brine, dried over K₂CO₃, filtered and concentrated under reduced pressure to give the title compound (1.01g).

25

Intermediate 74

4''-O-propenyl-6-O-propyl-erythromycin A

30 The intermediate 73 (1.01 g) was dissolved in MeOH (50 mL) and was stirred at room temperature for 20 h. The solvent was removed under reduce pressure and DCM (50 mL) and water (30 mL) were added. The pH was adjusted at 9.5 by addition of NaOH (1M) and the organic phase was dried over K₂CO₃, filtered and evaporated under reduced pressure affording the title compound (0.92 g).

MS; m/z (ES): 830.6 [MH]⁺.

Intermediate 75

11,12-carbonate-2',4''-O-diacetyl-11,12-dideoxy-6-O-methyl-erythromycin A

40 To a solution of 2',4''-O-diacetyl-6-O-methyl-erythromycin A (200 g) in anhydrous DCM (1.6 L), pyridine (117 mL) and a solution of triphosgene (71.2 g) in DCM (400 mL) were added at 0°C under a nitrogen atmosphere. The resulting mixture was stirred at 0°C for 30 min and then at room temperature for 15 h. The mixture was then diluted with water (750 mL) and extracted with DCM (2x500 mL). The organic phase was washed with water (3x300 mL), dried, filtered and evaporated under reduced pressure to give the title compound (200 g). MS; m/z (ES): 858 [MH]⁺.

Intermediate 76**11-deoxy-2',4''-O-diacetyl-10,11-didehydro-6-O-methyl-erythromycin A**

To a solution of intermediate 75 (50.5 g) in 2/1 mixture of anhydrous toluene/EtOAc (675 mL), DBU (9.24 mL) was added at room temperature. The resulting mixture was heated to 85°C for 8 h. A further addition of DBU (4.4 mL) was performed and the reaction mixture was stirred at room temperature for 5 h. The mixture was then diluted with brine (250 mL), extracted with EtOAc (2x350 mL) dried, filtered. Solvent evaporation of under reduced pressure and crystallisation from acetone/water gave the title compound (46 g).

MS; m/z (ES): 814 [MH]⁺.

Intermediate 77**12-chloroethanoyl-11-deoxy-2',4''-O-diacetyl-10,11-didehydro-6-O-methyl-erythromycin A**

To a solution of intermediate 76 (20 g) in anhydrous DCM (340 mL) at 0°C, pyridine (6 mL) and chloroacetic anhydride (8.4 g) were added and the reaction mixture was allowed to reach room temperature. After 16 h the reaction mixture was washed with water (300 mL) the organic phase was firstly washed with a saturated aqueous solution of NH₄Cl (150 mL) and then with brine (150 mL). The combined aqueous phase was extracted with DCM (2x300 mL). The organic phase was dried, filtered and evaporated under reduced pressure. The crude product was precipitated from acetone/water affording the title compound (20.4 g).

MS; m/z (ES): 890 [MH]⁺.

Intermediate 78**(11S, 11aR)-11-(carboxycyanomethyl)-11-deoxy-2',4''-O-diacetyl-6-O-methyl-erythromycin A**

Intermediate 77 (27.4g) was dissolved in anhydrous DMF (275 mL) and potassium cyanide (5 g) was added. The mixture was stirred at room temperature for 4.5 h, quenched with a saturated aqueous solution of NaHCO₃ (250 mL) and extracted with DCM (3x300 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was dissolved in acetone (100 mL) and the compound was precipitated by addition of water (250 mL). Filtration afforded the title compound (25.8 g).

MS; m/z (ES): 881 [MH]⁺.

Intermediate 79**(11S, 11aR)-11-(carboxycyanomethyl)-11-deoxy-6-O-methyl-erythromycin A**

To a solution of intermediate 78 (300 mg) in anhydrous MeOH (40 mL) was added an aqueous solution of lithium hydroxide (1M, 4 mL) and the reaction mixture was stirred at room temperature for 48 h. A solution of HCl (10% v/v) was slowly added to reach pH = 8, the solvent was partially evaporated under reduced pressure. The solution was diluted with water (20 mL) and extracted with DCM (8x20 mL). The collected organic phase was dried, over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent: DCM/MeOH 85/15) affording the title compound (150 mg).

MS; m/z (ES): 797 [MH]⁺.

TLC: MeOH/DCM 10/90 (Rf=0.23).

Intermediate 80

(11S, 11aR)-2'-O-acetyl-11-(carboxycyanomethyl)-11-deoxy-6-O-methyl-erythromycin

5 **A**

To a solution of intermediate 79 (150 mg) in anhydrous DCM (20 mL) NaHCO₃ (48 mg) was added followed by acetic anhydride (0.020 mL). The reaction mixture was stirred at room temperature overnight. The NaHCO₃ was filtered off, the organic phase was washed with water (3x20 mL), the combined organic phase was dried, filtered and concentrated under

10 reduced pressure yielding the title compound (0.145g).

MS; m/z (ES): 839 [MH]⁺.

TLC: MeOH/DCM 5/95 (Rf=0.24).

Intermediate 81

15 **(11S, 11aR)-2'-O-acetyl-4"-O-propenoyl-11-(carboxycyanomethyl)-11-deoxy-6-O-methyl-erythromycin A**

To a solution of intermediate 80 (90 mg) in anhydrous DCM (10 mL) cooled to 0°C pyridine (0.174 mL) was added followed by propenoyl chloride (0.174 mL). The reaction mixture was warmed to room temperature and stirred for 24 h, then washed with water (3x10 mL). The

20 organic phase was then firstly washed with a saturated aqueous solution of NaHCO₃ (2x10 mL) and then with brine (2x10 mL). The combined aqueous phase was extracted with DCM (2x10 mL) and the combined organic phase was dried, filtered and concentrated under reduced pressure. The crude material was filtered through a silica gel pad (eluent: DCM/MeOH 95/5) yielding the title compound (90 mg).

25 MS; m/z (ES): 893 [MH]⁺.

TLC: MeOH/DCM 5/95 (Rf=0.42).

Intermediate 82

2'-O-acetyl-roxithromycin

30 To a solution of roxithromycin (500 mg) and NaHCO₃ (150 mg) in anhydrous DCM (50 mL) acetic anhydride (0.062 mL) was added. The reaction mixture was stirred at room temperature overnight, filtered and the filtrate washed with water (3x20 mL). The combined aqueous phase was extracted with DCM (3x20 mL) and the combined organic phase was dried, filtered and concentrated under reduced pressure yielding the title compound (510 mg).

35 MS; m/z (ES): 879 [MH]⁺.

TLC: MeOH/DCM 5/95 (Rf=0.28).

Intermediate 83

2'-O-acetyl-4"-O-propenoyl-roxithromycin

40 To a solution of intermediate 82 (50 mg) in anhydrous toluene (10 mL), triethylamine (0.016 mL) and 3-chloropropionyl chloride (0.008 mL) were added. The reaction mixture was stirred at room temperature overnight. Water (3 mL) was added and the reaction mixture was extracted with EtOAc (3x10 mL). The combined organic phase was dried over Na₂SO₄,

filtered and concentrated under reduced pressure. The crude material was filtered through a silica gel pad (eluent: DCM/MeOH 95/5) yielding the title compound (49 mg).

MS; m/z (ES): 933 [MH]⁺.

TLC: MeOH/DCM 5/95 (R_f=0.36).

5

Intermediate 84

6-(2-amino-ethylamino)-7-chloro-1-cyclopropyl-1H-quinolin-4-one
and

7-(2-amino-ethylamino)-1-cyclopropyl-6-fluoro-1H-quinolin-4-one

10 A solution of a 40:60 mixture of intermediates 15 and 16 (147 mg) in aqueous HCl (2 N, 5 mL) was heated at 100°C for 4 days in a sealed tube. The reaction mixture was concentrated under reduced pressure. The crude product was purified by preparative TLC (eluent: DCM/MeOH/NH₄OH 90/10/1.5) to give the title compounds (23 mg, a 70/30 mixture of Cl/F derivatives).

15 ¹H-NMR (500 MHz) δ for 6-(2-amino-ethylamino)-7-chloro-1-cyclopropyl-1H-quinolin-4-one: 8.05 (s, 1H), 7.85 (d, 1H), 7.35 (s, 1H), 6.10 (d, 1H), 3.50-2.70 (m, 5H), 1.30-0.98 (m, 4H).

20 ¹H-NMR (500 MHz) δ for 7-(2-amino-ethylamino)-1-cyclopropyl-6-fluoro-1H-quinolin-4-one: 7.81 (d, 1H), 7.65 (d, 1H), 7.00 (d, 1H), 6.03 (d, 1H), 3.50-2.70 (m, 5H), 1.30-0.98 (m, 4H).

Intermediate 85

7-(2-amino-ethylamino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester

25 A suspension of intermediate 8 (2.0 g, 6.55 mmol) in 3% H₂SO₄ in MeOH (170 ml) was stirred at 60 °C for 48 h during which time the reaction mixture became a solution. The reaction solution was neutralised and the solvent was evaporated. The crude product was purified via flash chromatography on silica gel by using MeOH-CH₂Cl₂-NH₄OH=9-5-0.5 affording the title compound (720 mg).

30

Intermediate 86

7-[(2-aminobutyl)amino]-1-methyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

35 To a solution of 7-chloro-1-methyl-4-oxo-1,4-dihydro-3-quinoline carboxylic acid (1.0 g, prepared according to H. Agui and T. Nakagome, J. Heterocycl. Chem., (1979), 16(7), 1353-60) in 1-methyl-2-pyrrolidinone (10 mL), was added 1,4-diaminobutane (1.84 g). The mixture was heated at 130°C for 17 hours. The reaction mixture was cooled and poured into DCM (20 mL). The precipitate obtained was dispersed in MeOH and filtered to give the title compound (860 mg).

MS (ES) m/z: [MH]⁺ 290.3.

40

Intermediate 87

7-[(2-aminoethyl)amino]-1-methyl-4-oxo-1,4-dihydro-3-quinoline carboxylic acid

To a solution of 7-chloro-1-methyl-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid (1.5 g, prepared according to H. Agui and T. Nakagome, J. Heterocycl. Chem., (1979), 16(7), 1353-

60) in 1-methyl-2-pyrrolidinone (15 mL), was added ethylenediamine (1.9 g). The mixture was heated at 130°C for 24 hours. The reaction mixture was cooled and poured into DCM (20 mL). The precipitate obtained was dispersed in MeOH, filtered giving the title compound (500 mg).

5 MS (ES) m/z: [MH]⁺ 262.3.

Intermediate 88

7-[(2-aminoethyl)amino]-1-cyclopropyl-1,4-dihydro-4-oxo-6-fluoro-8-methoxy-3-quinoline carboxylic acid

10 To a solution of 1-cyclopropyl-1,4-dihydro-4-oxo-6,7-difluoro-8-methoxy-3-quinoline carboxylic acid (1.0 g) in N,N-dimethylacetamide (10 ml), N-BOC-ethylenediamine (0.82 mg) was added. The mixture was heated at 120°C for 12h. Trifluoroacetic acid (20 ml) was added and the reaction mixture was stirred at r.t. for 24 h. The solvent was evaporated under reduced pressure. The crude product was dissolved in water (5ml) and pH adjusted with 20%
15 NaOH to 7. The precipitate obtained was dispersed in MeOH and filtered to give the title compound (1,01 g).

MS; m/z (ES): 336.0 [MH]⁺.

Example 1

4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-8a-aza-8a-homoerythromycin A

To a solution of intermediate 23 (20 mg) in CH₃CN (0.4 mL) was added intermediate 7 (16 mg). The resulting mixture was heated at 70°C for 24 h. The solvent was concentrated under reduced pressure and the residue was purified by silica SPE-column using a gradient solvent
25 system DCM/MeOH/NH₄OH affording the title compound (11 mg).

MS; m/z (ES): 1124.5 [MH]⁺.

¹H-NMR (500 MHz) δ: 8.73 (s, 1H), 8.05 (s, 1H), 7.53 (s, 1H), 5.86 (br.s, 1H), 5.31 (t, 1H), 5.12 (d, 1H), 4.91 (dd, 1H), 4.70 (d, 1H), 4.53 (d, 1H), 4.33 (m, 2H), 4.19 (m, 1H), 3.83 (m, 1H), 3.76-3.70 (m, 1H), 3.68-3.64 (m, 1H), 3.58-3.55 (m, 2H), 3.49 (s, 1H), 3.39 (m, 1H),
30 3.29 (s, 3H).

Example 2

4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl) amino]ethyl]amino]propionyl]-8a-aza-8a-homoerythromycin A

35 To a solution of intermediate 23 (20 mg), in MeOH (0.4 mL), intermediate 8 (36 mg) was added. The resulting mixture was heated at 70°C in an ultrasonic bath for 60 h. The mixture was filtered and the filtrate evaporated under reduced pressure. The residue was purified by silica SPE-column (eluent: from DCM 100% to DCM/MeOH/NH₄OH 85/13/2) to afford the title compound (13.6 mg).

40 Ms (ES) m/z: 1108 [MH]⁺.

Example 3

4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A

To a solution of intermediate 25 (5 g) in i-PrOH (40 mL) intermediate 7 (2.8 g) was added. Reaction mixture was stirred at 80 °C for 24 h. Excess of amine was filtered from the reaction mixture and MeOH (100 mL) was added. The reaction mixture was stirred for 4 days. Reaction mixture was filtered and evaporated under reduced pressure to give the crude product mixture (5.94 g). The crude product was purified by flash chromatography in gradient solvent system DCM/MeOH/NH₄OH to give the title compound (1.385 g).

MS; m/z (ES): 1139.8 [MH]⁺.

¹H-NMR (500 MHz) δ: 8.73 (s, 1H), 8.04 (s, 1H), 7.54 (s, 1H), 5.61 (d, 1H), 5.28 (t, 1H), 5.08 (d, 1H), 4.94 (dd, 1H), 4.70 (d, 1H), 4.50 (d, 1H), 4.37 (m, 1H), 4.19 (m, 1H), 3.98 (d, 1H), 3.71-3.66 (m, 2H), 3.58-3.54 (m, 1H), 3.50 (s, 1H), 3.38 (m, 1H), 3.31 (s, 3H).

¹³C-NMR (75 MHz) δ: 177.5; 177.2; 174.3; 172.3; 167.3; 145.8; 143.1; 132.5; 127.6; 126.3; 118.0; 107.6; 104.5; 102.6; 95.3; 80.1; 78.9; 78.8; 77.4; 74.2; 72.9; 70.8; 70.3; 68.2; 65.4; 62.8; 51.8; 49.5; 47.5; 45.5; 44.4; 43.0; 42.8; 42.4; 42.3; 40.9; 40.4; 35.3; 35.1; 34.7; 29.0; 23.9; 21.7; 21.6; 21.3; 21.2; 18.0; 16.1; 15.0; 11.2; 9.6; 9.3; 8.1.

Example 4

4''-O-[3-[2-[3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A

To a solution of intermediate 26 (134 mg) in i-PrOH (2.5 mL) intermediate 8 was added (100 mg) and shaken at 85°C for 14 days. The reaction mixture was cooled to room temperature and filtered through silica gel cartridge (2 g) eluting with DCM (10 mL). The solvent was evaporated to give 100 mg of crude residue that was purified by silica SPE-column in gradient solvent system DCM/MeOH/NH₄OH affording the title compound (9,3 mg).

MS; m/z (ES): 1122.3 [MH]⁺.

Example 5

4''-O-[3-[2-[7-chloro-1-cyclopropyl-1,4-dihydro-3-methoxycarbonyl-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A

To a solution of intermediate 25 (100 mg) in i-PrOH (1 mL) intermediate 10 (60 mg) was added. This mixture was heated at 70°C for 18 h. The solvent was evaporated and the residue was dissolved in MeOH and stirred at room temperature for 24 h. The solvent was evaporated and the residue purified by silica gel SPE-column (eluent: from DCM 100% to DCM/MeOH/NH₄OH 85/13/2) affording the title compound (62 mg).

MS; m/z (ES): 1152.6 [MH]⁺.

Example 6

4''-O-[3-[4-(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)-1-piperazinyl]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A

A mixture of intermediate 26 (100 mg) and 1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-piperazinyl-quinoline-3-carboxylic acid (203 mg) in MeOH (20 mL) was stirred at 60 °C for 2 days, then at room temperature for 2 days and then at 60°C for 24 h. Isocyanate polymer-bound (600 mg) and DCM (60 mL) were added and stirred at room temperature for 48 h. The suspension was filtered and washed with DCM (10 mL). The filtrate was concentrated under reduced pressure affording the title compound (150 mg).

MS; m/z (ES): 1149.4 [MH]⁺.

Example 7

4''-O-[3-[4-(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-

quinoliny]piperazinyl]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A

According to the same procedure described for example 6, reaction of intermediate 26 (10 mg) and 1-cyclopropyl-4-oxo-7-piperazinyl-1,4-dihydro-quinoline-3-carboxylic acid (19 mg) afforded the title compound (4.2 mg).

MS; m/z (ES): 1131.6 [MH]⁺.

Example 8

4''-O-[3-[4-(1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)-

piperazinyl]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A

According to the same procedure described for example 6, reaction of intermediate 26 (10 mg) and 1-cyclopropyl-5-fluoro-4-oxo-7-piperazinyl-1,4-dihydro-4-quinolinone (18 mg) afforded the title compound (5.1 mg).

MS; m/z (ES): 1105.6 [MH]⁺.

Example 9

4''-O-[3-[4-(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)-1-

pyperazinyl]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A

According to the same procedure described for example 6, reaction of intermediate 26 (10 mg) and 7-chloro-1-cyclopropyl-4-oxo-6-piperazinyl-1,4-dihydro-quinolone-3-carboxylic acid (21 mg) afforded the title compound (4.8 mg).

MS; m/z (ES): 1165.8 [MH]⁺.

Example 10

4''-O-[3-[4-[3-(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-

quinoliny]amino]butyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A

To a solution of intermediate 26 (100 mg) in i-PrOH (2 mL), 7-((4-aminobutyl)amino)-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid (61 mg) was added and shaken at 70°C for 2 days. The solvent was evaporated and the residue was purified by flash chromatography in gradient solvent system DCM/MeOH/NH₄OH to give the title compound (48 mg).

MS m/z (ES): 1150.9 [MH]⁺.

Example 11

4''-O-[3-[3-[3-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-

quinoliny]amino]propyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A

To a solution of intermediate 25 (10 mg) in i-PrOH (3 mL) was added intermediate 14 (17 mg) and the reaction mixture was heated at 70°C for 42 h. The reaction mixture was filtered washing the solid with i-PrOH, the combined filtered were concentrated under reduced pressure and stirred in MeOH for 72 h. Solvent evaporation gave the crude product which

was purified by preparative TLC (eluent: MeOH/NH₄OH 97/3) affording the title compound (3.6 mg).

¹H-NMR (500MHz) δ: 8.73 (s, 1H), 7.93 (d, 1H), 7.00 (bm, 1H), 6.91 (d, 1H), 5.60 (bd, 1H), 4.70 (d, 1H), 4.40 (m, 1H), 4.20 (m, 1H), 3.50 (m, 1H), 3.40 (m, 2H), 2.94-2.90 (m, 4H), 2.65 (m, 2H), 1.95 (m, 2H), 1.39 (m, 2H), 1.16 (m, 2H).

Example 12

4''-O-[3-[[3-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]propyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A

To a solution of intermediate 25 (10 mg) in i-PrOH (3 mL) was added intermediate 13 (20 mg) and the reaction mixture was heated at 70°C for 42 h. The reaction mixture was filtered washing the solid with i-PrOH, the combined filtered were concentrated under reduced pressure and stirred in MeOH for 72 h. Solvent evaporation gave the crude product which was purified by preparative TLC (eluent: MeOH/NH₄OH 97/3) affording the title compound (3.9 mg).

¹H-NMR (500MHz) δ: 8.73 (s, 1H), 8.02 (s, 1H), 7.52 (s, 1H), 5.86 (bs, 1H), 5.59 (bd, 1H), 4.70 (d, 1H), 4.38 (m, 1H), 3.55 (m, 1H), 3.40 (m, 2H), 2.93 (m, 2H), 2.85 (m, 2H), 2.71-2.55 (m, 2H), 2.00 (m, 2H), 1.40 (m, 2H), 1.16 (m, 2H).

Example 13

4''-O-[3-[(2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl)amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A

To solution of intermediate 26 (100 mg) in i-PrOH (1 mL), intermediate 4 (105 mg) was added and shaken at 70°C for 22 h. The solvent was evaporated, and the residue was triturated with DCM (2 mL). The resulting suspension was filtered and washed with DCM (1 mL). The filtrate was concentrated under reduced pressure. The crude product was precipitated from EtOAc/n-hexane affording the title compound (20 mg).

MS; m/z (ES): 1105.0 [MH]⁺.

Example 14

4''-O-[3-[[2-[(3-carboxy-1,4-dihydro-1-ethyl-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A

A solution of intermediate 26 (90 mg) and intermediate 3 (90 mg) in i-PrOH (1 mL) was heated at 70°C for 20 h. The solvent was evaporated, the residue was triturated with DCM (2 mL). The resulting suspension was filtered and washed with DCM (1 mL). The mother liquor was concentrated under reduced pressure. The crude product was precipitated from EtOAc/n-hexane affording the title compound (38 mg).

MS; m/z (ES): 1093.3 [MH]⁺.

Example 15

4''-O-[3-[4-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-1,8)naphthyridinyl]-4-oxo-[1-piperazinyl]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A

To a solution of intermediate 25 (20 mg) in anhydrous MeOH (2 mL) 1-ethyl-6-fluoro-4-oxo-7-piperazin-1-yl-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (22 mg) was added. The

reaction mixture was stirred at 40°C overnight, the solvent was evaporated and the residue dissolved in DCM (3 mL). Isocyanate polymer-bound resin was added and the mixture was shaken at room temperature overnight. The resin was filtered and washed with DCM (3 mL), MeOH (3 mL) and DCM (3 mL). The collected organic extracts were evaporated under reduced pressure. The residue was dissolved in DCM (5 mL) and washed with water (3x3 mL). The organic phase was dried, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 90/10) affording the title compound (18 mg).

¹H-NMR (500MHz) δ: 15.0 (bs, 1H), 8.71 (s, 1H), 8.12 (d, 1H), 5.57 (bd, 1H), 4.72 (d, 1H), 4.41 (q, 2H), 4.39 (m, 1H), 4.19 (m, 1H), 3.85 (m, 4H), 2.83-2.55 (m, 4H), 2.64 (m, 4H), 1.51 (t, 3H).

Example 16

4''-O-[3-[(2-[(1-benzyl-3-carboxy-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl)amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A

To a solution of intermediate 26 (80 mg) in i-PrOH (1.5 mL) was added intermediate 1 (49 mg). The resulting mixture was stirred at 70°C for 18 h. DBU (0.04 mL) was added and the reaction mixture was stirred at 50°C for additional 24 h. The solvent was evaporated under reduced pressure, and the crude product was purified by flash chromatography (eluent: MeOH/DCM/NH₄OH 9/90/1.5) affording the title compound (30 mg).

MS; m/z (ES): 1154.2 [MH]⁺.

Example 17

4''-O-[3-[(2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl)amino]propionyl]-6-O-ethyl-8a-aza-8a-homoerythromycin A

To a solution of intermediate 30 (139 mg) in MeOH (5 mL) was added intermediate 7 (102.5 mg) and stirred at 60°C for 24 h. The reaction suspension was filtered, concentrated under reduced pressure and the residue purified by flash chromatography (eluent: DCM/MeOH/NH₄OH 9/1.3/0.2) affording the title compound (37 mg).

MS; m/z (ES): 1153.7 [MH]⁺.

¹³C-NMR (500 MHz) (δ/ppm): 177.5, 175.2, 172.3, 167.4, 145.8, 143.1, 132.5, 127.6, 126.3, 118.0, 107.6, 104.5, 103.1, 97.4, 78.8, 78.7, 77.5, 74.1, 73.1, 71.0, 70.9, 68.6, 65.4, 62.9, 49.5, 47.5, 45.4, 44.5, 42.8, 42.5, 41.9, 41.8, 40.7, 40.4, 35.8, 35.4, 34.5, 23.2, 21.5, 21.4, 21.3, 17.5, 16.1, 15.4, 10.8, 10.5, 9.9, 8.1.

Example 18

4''-O-[3-[(2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl)amino]propionyl]-6-O-propyl-8a-aza-8a-homoerythromycin A

To a solution of intermediate 48 (220 mg) in MeOH (5 mL) was added intermediate 7 (182 mg) stirred at 60°C for 24 h. The reaction suspension was filtered, methanol was evaporated under reduced pressure and the residue was purified by flash chromatography (eluent: DCM/MeOH/NH₄OH 85/13/2) affording the title compound (23 mg).

MS; m/z (ES): 1167.3 [MH]⁺.

¹³C-NMR (500 MHz) (δ/ppm): 177.5, 175.1, 172.2, 167.4, 145.8, 143.1, 132.5, 127.7, 126.4, 118.0, 107.6, 104.4, 102.9, 97.3, 78.9, 78.7, 77.4, 74.2, 73.0, 71.1, 70.9, 68.5, 65.4, 62.9, 49.5, 47.5, 45.4, 44.5, 42.8, 42.5, 42.0, 40.7, 40.4, 35.8, 35.4, 34.6, 23.2, 21.6, 21.5, 21.4, 21.3, 17.6, 16.2, 16.0, 10.8, 10.5, 9.9, 8.1.

5

Example 19

11,12-carbonate-4''-O-[[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]carbonyl]-11,12-dideoxy-6-O-methyl-8a-aza-8a-homoerythromycin A

10 To a solution of intermediate 36 (105 mg) in DMF intermediate 7 (73 mg) and DBU (0.2 mL) were added. The resulting mixture was stirred under argon atmosphere at 60°C for 1 h. Then EtOAc (30 mL) and a saturated aqueous solution of NaHCO₃ (30 mL) were added. The aqueous phase was washed with EtOAc (2x15 mL), and the organic solutions were combined, dried and concentrated under reduced pressure.

15 The crude residue was dissolved in MeOH (50 mL) and the solution was stirred overnight. The solvent was evaporated, and the crude product was purified by flash chromatography (eluent: MeOH/DCM/NH₄OH 9/90/1.5) affording the title compound (80 mg).

¹H-NMR (500 MHz) δ: 8.73 (s, 1H), 8.06 (s, 1H), 7.49 (s, 1H), 6.22 (d, 1H), 5.40 (t, 1H), 5.32 (t, 1H), 5.03 (d, 1H), 4.93 (dd, 1H), 4.60 (d, 1H), 4.41 (d, 1H), 4.38 (d, 1H), 4.34 (m, 1H), 4.13 (m, 1H), 4.02 (m, 1H), 3.67-3.62 (m, 3H), 3.57-3.55 (m, 2H), 3.47-3.43 (m, 2H), 3.31 (s, 3H), 3.18 (s, 3H).

20 ¹³C-NMR (75 MHz) δ: 177.5; 176.4; 170.4; 167.3; 157.5; 153.3; 145.9; 142.9; 132.7; 127.5; 126.2; 118.1; 107.6; 103.9; 102.9; 96.1; 85.6; 82.2; 80.38; 79.7; 79.6; 75.4; 73.2; 70.7; 68.7; 65.3; 63.1; 51.1; 49.6; 45.8; 45.05; 42.6; 42.4; 42.0; 40.3; 39.8; 35.4; 29.1; 22.8; 22.5; 21.9; 21.3; 21.1; 17.7; 14.6; 14.0; 12.3; 11.0; 10.5; 8.1.

25

Example 20

4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl) amino]ethyl]amino]propionyl]-11-O-[3-(3-quinolyl)-2-propenyl]-8a-aza-8a-homoerythromycin A

30

To a suspension of intermediate 40 (0.1 g) in i-PrOH (4 mL) intermediate 7 (0.2 g) was added. The resulting mixture was stirred at 80°C for 3 days, then the solvent was evaporated and the residue was purified by flash chromatography (eluent: CHCl₃/MeOH/NH₄OH 6/1/0.1) affording the title compound (45 mg).

35 MS; m/z (ES): 1291.9 [MH]⁺.

Example 21

4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino] ethyl]amino] propionyl]-6-O-methyl-9a-aza-9a-homoerythromycin A

40

To a solution of intermediate 43 (200 mg) in i-PrOH (2 mL) was added intermediate 7 (125 mg) and shaken for 7 h at 70°C, then at 80°C overnight. The reaction was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography in gradient solvent system DCM/MeOH/NH₄OH to afford the title compound (48 mg).

MS; m/z (ES): 1139.8 [MH]⁺.

Example 22

4''-O-[3-[[4-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-

quinolinyl)amino]butyl]amino]propionyl]-6-O-methyl-9a-aza-9a-homoerythromycin A

To a solution of intermediate 43 (100 mg) in i-PrOH (2 mL), 7-((2-aminobutyl)amino)-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid (122 mg) was added and shaken at 70°C for 24 h. The solvent was concentrated under reduced pressure. The residue was purified by flash chromatography in gradient solvent system DCM/MeOH/NH₄OH

affording the title compound (34 mg).

MS; m/z (ES): 1150 [MH]⁺.

Example 23

4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-

quinolinyl)amino]ethyl]amino]propionyl]-6-O-ethyl-9a-aza-9a-homoerythromycin A

To a solution of intermediate 45 (200 mg) in methanol (5 mL) intermediate 7 (148 mg) was added and stirred at 60 °C for 24 h. The reaction suspension was filtered, methanol was evaporated under reduced pressure and the residue was purified by flash chromatography (eluent: DCM/MeOH/NH₄OH 9/1.3/0.2) affording the title compound (34 mg).

MS; m/z (ES): 1153.0 [MH]⁺.

¹³C-NMR (500 MHz, δ): 179.2, 177.1, 172.2, 167.4, 145.9, 143.1, 132.5, 127.6, 126.3, 118.0, 107.6, 104.5, 101.3, 96.1, 80.0, 79.0, 78.6, 77.7, 74.2, 73.8, 72.8, 71.3, 67.3, 65.0, 63.3, 58.9, 50.8, 49.4, 47.6, 45.6, 44.5, 42.8, 40.6, 40.4, 39.8, 35.4, 35.2, 34.7, 34.3, 21.7, 21.3, 20.8, 20.7, 18.6, 18.3, 16.4, 16.1, 15.9, 11.2, 9.7, 8.1.

Example 24

4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)-amino]ethyl]amino]propionyl]-6-O-propyl-9a-aza-9a-homoerythromycin A

To a solution of intermediate 48 (100 mg) in methanol (5 mL) intermediate 7 (73 mg) was added and stirred at 60°C for 24 h. The reaction suspension was filtered, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (eluent: DCM/MeOH/NH₄OH 9/1.3/0.2) affording the title compound (10 mg).

MS; m/z (ES): 1167.3 [MH]⁺.

Example 25

11,12-carbonate-4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-11,12-dideoxy-azithromycin

To a suspension of intermediate 50 (1.0 g) in i-PrOH (45 mL) intermediate 7 (2.0 g) was added. This mixture was heated at 70°C for 48 h. The solvent was evaporated and the residue purified by flash chromatography (eluent: CHCl₃/MeOH/NH₃ 6/1/0.1) affording the title compound (120 mg).

MS; m/z (ES): 1151 [MH]⁺.

¹H-NMR (500MHz) δ : 8.72 (s, 1H), 8.04 (s, 1H), 7.52 (s, 1H), 5.10 (d, 1H), 4.87 (dd, 1H), 4.72 (d, 1H), 4.48 (d, 1H), 4.44-4.37 (m, 3H), 3.70 (m, 1H), 3.58 (d, 1H), 3.31 (s, 3H), 3.27

(m, 1H), 2.87-2.84 (m, 2H), 2.67-2.55 (m, 3H), 2.44-2.36 (m, 8H), 2.21 (s, 3H), 2.07 (m, 1H), 2.00 (m, 1H), 1.92 (m, 1H), 1.87-1.79 (m, 2H), 1.68-1.55 (m, 3H), 1.45 (s, 3H).

Example 26

5 11,12-carbonate-4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)amino]ethyl]amino]propiony]-11,12 dideoxy azithromycin

To a suspension of intermediate 50 (1.0 g) in i-PrOH (45 mL) intermediate 8 (2.0 g) was added. This mixture was heated at 70°C for 48 h. The solvent was evaporated and the residue was purified by flash chromatography (eluent: CHCl₃/MeOH/NH₃ 6/1/0.1) affording the title compound (150 mg).

MS; m/z (ES): 1135 [MH]⁺.

Example 27

15 11,12-carbonate-4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]-amino]propiony]-11,12-dideoxy-azithromycin

To a suspension of intermediate 50 (200 mg) in MeOH (2 mL) intermediate 4 (210 mg) was added. This mixture was heated at 70°C for 20 h. The solvent was removed under reduced pressure then DCM (10 mL) was added and the precipitate was filtered off. The organic phase was evaporated under reduced pressure and the residue purified by flash chromatography (eluent: CHCl₃/MeOH/NH₃ 6/1/0.1) affording the title compound (55 mg).

MS; m/z: (ES): 1117 [MH]⁺.

¹H-NMR (500MHz) δ: 8.56 (s, 1H), 8.11 (d, 1H), 6.88 (s, 1H), 6.81 (d, 1H), 5.12 (d, 1H), 4.88 (dd, 1H), 4.73 (d, 1H), 4.47-4.41 (m, 3H), 3.68 (m, 1H), 3.57 (d, 1H), 3.31 (s, 3H), 3.29 (dd, 1H), 3.04 (m, 4H), 2.87-2.86 (m, 2H), 2.68-2.63 (m, 3H), 2.44-2.35 (m, 8H), 2.30 (s, 3H), 2.06 (t, 1H), 1.99 (m, 1H), 1.93 (m, 1H), 1.83 (m, 1H), 1.74 (br d, 1H), 1.66-1.57 (m, 3H), 1.45 (s, 3H).

Example 28

30 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propiony]-azithromycin

To a suspension of intermediate 51 (70 mg) in acetonitrile (10 mL), intermediate 7 (60 mg) and DBU (0.05 mL) were added. This mixture was heated at 70°C for 18 h. The solvent was evaporated and the residue purified by flash chromatography (eluent: DCM/MeOH/NH₃ 90/9/1.5) affording the title compound (13 mg).

MS; m/z (ES): 1125 [MH]⁺.

¹³C-NMR (75 MHz) δ: 178.5; 176.8; 171.7; 166.8; 145.2; 142.5; 131.9; 127.0; 125.6; 117.5; 106.8; 103.7; 101.8; 82.4; 78.2; 77.1; 76.9; 73.5; 73.0; 72.7; 72.3; 70.3; 69.4; 67.3; 64.9; 62.4; 62.0; 48.9; 46.9; 44.7; 43.8; 42.2; 41.9; 41.5; 39.8; 35.5; 34.8; 34.2; 34.0; 28.4; 27.0; 26.1; 21.4; 21.3; 20.7; 20.6; 17.1; 15.7; 13.8; 10.6; 8.3; 7.5; 6.5.

Example 29

40 4''-O-[[[4-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)amino]butyl]amino]carbonyl]azithromycin

To a solution of intermediate 52 (130 mg) in DMF (1 mL) 7-((2-aminobutyl)amino)-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid (54 mg) and DBU (0.2 mL) were added. The reaction mixture was stirred at room temperature for 24 h. Then EtOAc (30 mL) and H₂O (20 mL) were added. The pH of the reaction mixture was adjusted to 9.5 by addition of NaOH (1M). The layers were separated, and the aqueous layer was washed with EtOAc (2x5 mL). The combined organic layers were concentrated under reduced pressure. The residue was dissolved in MeOH (20 mL) and stirred at 60°C for 4 h and then at room temperature overnight. The solvent was evaporated and the residue purified by flash chromatography (eluent DCM/MeOH/NH₄OH 90/10/1.5) affording the title compound (49 mg).

MS; m/z (ES): 1109.54 [MH]⁺.

¹H-NMR (500 MHz) δ: 8.69 (s, 1H), 7.91 (d, 1H), 7.00 (d, 1H), 5.18 (d, 1H), 5.12 (brs, 1H), 4.96 (brs, 1H), 4.71 (dd, 1H), 4.55 (d, 1H), 4.53 (d, 1H), 4.34 (m, 1H), 4.24 (d, 1H), 3.76 (m, 1H), 3.66 (s, 1H), 3.60 (d, 1H), 3.54 (m, 1H).

¹³C-NMR (125 MHz) δ: 178.2; 176.3; 166.9; 156.0; 151.2; 147.9; 146.2; 141.9; 141.8; 139.7; 109.5; 109.3; 107.1; 101.6; 95.2; 94.1; 83.12; 78.5; 77.4; 73.6; 73.0; 72.9; 72.7; 70.4; 69.4; 67.0; 64.8; 62.8; 62.1; 48.9; 44.7; 42.0; 41.6; 41.5; 39.9; 39.7; 35.6; 34.8; 34.4; 27.1; 29; 26.9; 26.2; 25.2; 21.4; 20.9; 20.6; 20.5; 17.2; 15.6; 14.1; 10.6; 8.7; 7.7; 6.7.

20 Example 30

4''-O-[[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]carbonyl]-azithromycin

To a solution of intermediate 52 (150 mg) in DMF (2 mL) intermediate 7 (65 mg) and DBU (0.4 mL) were added. The reaction mixture was stirred at room temperature for 24 h then EtOAc (30 mL) and H₂O (20 mL) were added. The pH of the reaction mixture was adjusted to 9.5 by addition of NaOH (1M). The layers were separated, and the aqueous layer was extracted with EtOAc (2x15 mL). The combined organic layers were concentrated under reduced pressure. The residue was dissolved in MeOH (20 mL) and stirred at 60°C for 4 h, then at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (eluent DCM/MeOH/NH₄OH 90/10/1.5) affording the title compound (60 mg).

MS; m/z (ES): 1097.1 [MH]⁺.

¹H-NMR (300 MHz, CDCl₃) δ: 8.72 (s, 1H), 8.05 (s, 1H), 7.47(s, 1H), 5.39 (t, 1H), 5.25 (m, 1H), 5.18 (d, 1H), 4.70 (dd, 1H), 4.59 (d, 1H), 4.51 (d, 1H), 4.36 (m, 1H), 4.25 (bs, 1H).

¹³C-NMR (75 MHz, CDCl₃) δ: 178.8; 177.5; 167.3; 157.7; 145.8; 142.9; 132.6; 127.5; 126.2; 118.2; 107.6; 103.7; 102.4; 94.7; 83.3; 79.7; 77.9; 74.2; 73.7; 73.6; 73.2; 70.9; 70.1; 67.8; 65.5; 63.3; 62.5; 49.5; 45.2; 45.1; 42.2; 42.0; 40.4; 39.8; 36.3; 35.4; 35.1; 29.5; 27.5; 26.7; 21.9; 21.6; 21.3; 21.2; 17.8; 16.2; 14.7; 11.3; 9.2; 8.2; 7.4.

40 Example 31

4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-3-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-azithromycin

To a solution of intermediate 54 (15 mg) in acetonitrile (0.6 mL) intermediate 7 (11.8 mg) and DBU (0.010 mL) were added. The mixture was stirred for 12h at 80°C. The solvent was

evaporated under reduced pressure and the residue was purified by silica SPE-column (eluent: from DCM 100% to DCM/MeOH/NH₄OH 85/13/2) affording the title compound (2.2 mg). MS; m/z (ES): 1138.7 [MH]⁺.

5 **Example 32**

11,12-(aminocarbonyloxy)-4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl]amino]propionyl]-11,12-dideoxy-6-O-methyl-erythromycin A

10 To a solution of intermediate 57 (20 mg) in acetonitrile (0.40 mL) intermediate 7 (15 mg) was added. This mixture was heated at 70°C for 12 h. DBU (0.030 mL) was added and the reaction mixture was stirred at the same temperature for additional 3 h. The solvent was evaporated and the residue purified by flash chromatography (eluent: from DCM 100% to DCM/MeOH/NH₄OH 85/13/2) affording the title compound (5.8 mg).

MS; m/z (ES): 1148.8 [MH]⁺.

15 ¹H-NMR (500 MHz) δ: 8.71 (s, 1H), 8.03 (s, 1H), 7.52 (s, 1H), 5.8 (s, 1H), 5.33 (bt, 1H), 5.10 (dd, 1H), 4.97 (d, 1H), 4.70 (d, 1H), 4.58 (d, 1H), 4.23-4.38 (m, 1H), 3.79 (d, 1H), 3.71-3.74 (m, 1H), 3.67 (s, 1H), 3.61 (d, 1H), 3.58 (d, 1H), 3.43 (m, 1H), 3.31 (s, 3H).

Example 33

20 **11,12-(aminocarbonyloxy)-4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-11,12-dideoxy-6-O-methyl-erythromycin A**

25 To a solution of intermediate 57 (20 mg) in acetonitrile (0.40 mL) the intermediate 8 (15 mg) was added. This mixture was heated at 70°C for 12 h. DBU (30 mL) was added and stirred at the same temperature for additional 3 h. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (eluent: from DCM 100% to DCM/MeOH/NH₄OH 85/13/2) affording the title compound (4.0 mg).

MS; m/z (ES): 1132.4 [MH]⁺.

30 **Example 34**

4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-11,12-dideoxy-6-O-methyl-11,12-(methylaminocarbonyloxy)-erythromycin A

35 To a solution of intermediate 59 (100 mg) in i-PrOH (2 mL) intermediate 7 (60 mg) and DBU (0.02 mL) were added. This mixture was heated at 70°C for 36 h, then the solvent was evaporated and the residue purified by flash chromatography (eluent: DCM/MeOH/NH₄OH 90/10/1.5) affording the title compound (39 mg).

MS; m/z (ES): 1162 [MH]⁺.

40 ¹H-NMR (500 MHz) δ: 8.73 (s, 1H), 8.04 (s, 1H), 7.54 (s, 1H), 5.27 (t, 1H), 4.96 (m, 2H), 4.70 (d, 1H), 4.56 (d, 1H), 4.34 (m, 1H), 3.75 (d, 1H), 3.72 (m, 1H), 3.63 (d, 1H), 3.56 (m, 1H), 3.54 (s, 1H).

¹³C-NMR (75MHz) δ: 215.8; 177.5; 176.6; 172.2; 167.3; 157.7; 145.98; 143.1; 132.5; 127.6; 126.3; 118.0; 107.6; 104.5; 102.1; 95.9; 82.8; 79.8; 78.7; 78.6; 77.6; 75.9; 72.7; 71.0; 67.8;

65.2; 63.0; 62.0; 50.2; 49.6; 47.6; 45.5; 45.2; 44.4; 42.8; 40.3; 38.9; 38.8 (2C); 35.4; 35.1; 34.6; 32.5; 21.9; 21.8; 21.2; 20.0; 18.6; 18.3; 15.9; 13.9; 13.7; 10.3; 9.1; 8.1.

Example 35

5 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]-methyl-amino]propionyl]-11,12-dideoxy-6-O-methyl-11,12-(methylaminocarbonyloxy)-erythromycin A

To a solution of example 34 (150 mg) in CHCl₃ (3 mL) formaldehyde (20 mL) and formic acid (18.2 mL) were added. This mixture was heated at 60°C for 10 h, then CHCl₃ (30 mL) and a saturated solution of NaHCO₃ (20 mL) were added. The aqueous phase was washed with CHCl₃ (15 mL) and the combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (eluent: DCM/MeOH/NH₄OH 90/10/1.5) affording of the title compound (76 mg).

MS; m/z (ES): 1176.8 [MH]⁺.

15 ¹H NMR (500 MHz, CDCl₃) δ: 8.73 (s, 1H), 8.05 (s, 1H), 7.51 (s, 1H), 5.33 (t, 1H), 4.98 (d, 1H), 4.95 (dd, 1H), 4.72 (d, 1H), 4.59 (d, 1H), 4.33 (m, 1H), 3.76 (d, 1H), 3.77-3.70 (m, 1H), 3.63 (d, 1H), 3.57 (m, 1H), 3.54 (s, 1H), 3.35 (m, 2H), 3.32 (s, 3H), 3.27 (m, 1H), 3.09 (s, 3H), 3.03 (m, 1H), 3.01 (s, 3H), 2.91 (m, 1H), 2.29 (s, 3H).

20 ¹³C NMR (125 MHz, CDCl₃) δ: 215.7; 177.6; 176.6; 171.8; 167.4; 145.8; 143.2; 132.5; 127.6; 126.3; 118.0; 118.0; 107.6; 104.5; 101.9; 95.9; 82.8; 79.9; 78.6; 78.5; 76.0; 72.8; 71.0; 67.7; 65.2; 63.0; 62.1; 55.4; 52.8; 50.2; 49.5; 45.5; 45.2; 41.3; 40.7; 38.9; 38.8; 35.4; 35.1; 32.7; 32.5; 21.9; 21.7; 21.1; 20.0; 18.5; 18.3; 15.9; 13.9; 13.7; 10.3; 9.2; 8.1.

MS; m/z (ES): 855 [MH]⁺.

25 Example 36

4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-11,12-dideoxy-11,12-(ethylaminocarbonyloxy)-6-O-methyl-erythromycin A

To a suspension of intermediate 64 (100 mg) in i-PrOH (2 mL) intermediate 7 (56 mg) and DBU (0.02 mL) were added. This mixture was heated at 70°C for 24 h then solvent was evaporated and the residue purified by flash chromatography (eluent: DCM/MeOH/NH₄OH 90/10/1.5) affording of the title compound (60 mg).

MS; m/z (ES): 1176.6 [MH]⁺.

35 ¹³C NMR (75 MHz, CDCl₃) δ: 216.1; 177.5; 176.3; 172.1; 167.3; 157.2; 145.9; 143.1; 132.6; 127.6; 126.3; 118.0; 107.6; 104.5; 102.0; 96.0; 82.6; 79.8; 78.7; 77.7; 76.1; 72.7; 71.0; 67.8; 65.2; 63.1; 60.0; 50.5; 49.5; 47.6; 45.6; 45.1; 44.4; 42.8; 40.4; 38.9; 38.8; 38.7; 38.6; 35.4; 35.1; 34.6; 29.5; 21.9; 21.8; 21.2; 20.1; 18.9; 18.3; 16.0; 14.2; 14.1; 12.5; 10.3; 9.2; 8.1.

Example 37

40 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-11,12-dideoxy-6-O-methyl-11,12-[(N-(4-phenylbutyl)amino)carbonyloxy]-erythromycin A

To a solution of intermediate 67 in i-PrOH (10 mL) and CH₃CN (2 mL) intermediate 7 (0.5 g) was added. This mixture was heated at 80°C for 24 h then the solvent was evaporated and the

residue purified by flash chromatography (eluent: DCM/MeOH/NH₄OH 90/10/1.5) affording the title compound (1.0 g).
MS; m/z (ES): 1281 [MH]⁺.

5 **Example 38**

4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A

To a suspension of intermediate 69 (500 mg) in acetonitrile (10 mL) were added intermediate 7 (300 mg) and DBU (0.4 mL). This mixture was heated at 70°C for 18 h. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (eluent DCM/MeOH/NH₄OH 90/10/1.5) affording of the title compound (370 mg).
MS; m/z (ES): 1124.7 [MH]⁺.

¹H-NMR (300 MHz) δ: 8.73 (s, 1H), 8.04 (s, 1H), 7.54 (s, 1H), 5.26 (t, 1H), 5.06 (dd, 1H), 4.99 (d, 1H), 4.70 (d, 1H), 4.57 (d, 1H), 4.34 (m, 1H).

15 ¹³C-NMR (75MHz) δ: 221.0; 177.5; 175.7; 172.2; 167.284, 145.8; 143.1; 132.5, 127.6; 126.3; 118.0; 107.7; 104.6; 102.2; 96.0; 80.4; 78.9; 78.8; 78.3; 78.2; 76.6; 74.3; 72.7, 71.1; 69.1; 67.8; 65.2; 63.0; 50.67.

Example 39

20 **4''-O-[3-[[2-[(3-carboxy-1,4-dihydro-1-ethyl-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A**

A solution of intermediate 69 (100 mg) and intermediate 3 (103 mg) in MeOH (1 mL) was shaken at 70°C for 16 h. The solvent was evaporated and the residue was triturated with DCM (2 mL). The solid material was filtered and washed with DCM (1 mL). The mother liquor was concentrated under reduced pressure. The crude product was precipitated from EtOAc/n-hexane 1/1 affording the title compound (10 mg).
MS; m/z (ES): 1077.8 [MH]⁺.

Example 40

30 **4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A**

A solution of intermediate 69 (100 mg) and intermediate 4 (107 mg) in MeOH (1 mL) was shaken at 70°C for 16 h. The solvent was evaporated and the residue was triturated with DCM (2 mL). The solid was filtered and washed with DCM (1 mL). The mother liquor was concentrated under reduced pressure. The crude product was precipitated from EtOAc/n-hexane 1/1 two times affording the title compound (15 mg).
MS; m/z (ES): 1090.8 [MH]⁺.

Example 41

40 **4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)amino]butyl]amino]propionyl]-6-O-methyl-erythromycin A**

To a solution of intermediate 69 (100 mg) in i-PrOH (2 mL) 7-((2-aminobutyl)amino)-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-quinoline-3-carboxylic acid (62 mg) was added. This mixture was heated at 80°C for 72 h then the solvent was evaporated and the residue purified

by flash chromatography (eluent: DCM/MeOH/NH₄OH 90/9/1.5) affording the title compound (141 mg).

MS; m/z (ES): 1136.1 [MH]⁺.

5 **Example 42**

4''-O-[3-[[2-[(3-carboxy-7-chloro-1,4-dihydro-1-ethyl-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A and 4''-O-[3-[[2-[(3-carboxy-1,4-dihydro-1-ethyl-6-fluoro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A

10 To a solution of intermediate 69 (133 mg) in i-PrOH (2 mL) intermediate 5 and intermediate 6 (100 mg, mixture 1/1) were added. The reaction mixture was heated at 80°C for 10 days. The solvent was evaporated and the residue purified by flash chromatography (eluent: DCM/MeOH/NH₄OH 90/9/1.5) affording the title compounds as 1/1 mixture (140 mg). MS; m/z (ES): 112.1 [MH]⁺; 1096.1 [MH]⁺.

15

Example 43

4''-O-[3-[[3-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)-amino]propyl]amino]propionyl]-6-O-methyl-erythromycin A

20 To a solution of intermediate 68 (10 mg) in i-PrOH (2.5 mL) intermediate 13 (20 mg) was added and the reaction mixture was heated at 70°C for 32 h. The reaction mixture was filtered washing the solid with i-PrOH. The combined solution was concentrated under reduced pressure and stirred in MeOH for 72 h. Solvent evaporation gave the crude product, which was purified by preparative TLC (eluent: MeOH/NH₄OH 97/3) affording the title compound (4.4 mg).

25 ¹H-NMR (500MHz) δ: 8.73 (s, 1H), 8.02 (d, 1H), 7.53 (bs, 1H), 5.83 (bs, 1H), 4.70 (d, 1H), 4.36 (m, 1H), 3.60-3.40 (m, 2H), 2.92 (m, 2H), 2.85 (m, 2H), 2.65 (m, 2H), 2.00 (m, 2H), 1.39 (m, 2H), 1.16 (m, 2H).

Example 44

30 **4''-O-[3-[[3-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)-amino]propyl]amino]propionyl]-6-O-methyl-erythromycin A**

To a solution of intermediate 68 (7 mg) in i-PrOH (2 mL) intermediate 14 (14 mg) was added and the reaction mixture was heated at 70°C for 32 h. The reaction mixture was filtered washing the solid with i-PrOH. The combined solution was concentrated under reduced pressure and stirred in MeOH for 72 h. Solvent evaporation gave the crude product which was purified by preparative TLC (eluent: MeOH/NH₄OH 97/3) affording the title compound (3.6 mg).

35 ¹H-NMR (500MHz) δ: 8.73 (s, 1H), 7.94 (d, 1H), 7.02 (bs, 1H), 6.91 (d, 1H), 4.70 (d, 1H), 4.36 (m, 1H), 3.50-3.30 (m, 4H), 2.96-2.88 (m, 4H), 2.70-2.55 (m, 2H), 1.39 (m, 2H), 1.16 (m, 2H).

40

Example 45

4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A

To a solution of intermediate 8 (50.4 mg) in anhydrous DMSO (1 mL), DIPEA (0.02 mL) was added and the reaction mixture was stirred at room temperature for 1 h. This mixture was added to a solution of intermediate 68 (50 mg) in DMSO (1 mL) and the reaction mixture was heated at 80°C for 12 h. The reaction mixture was cooled to room temperature and DCM (10 mL) was added followed by water (10 mL). The organic phase was washed with water (3x10 mL), dried, filtered and concentrated under reduced pressure. The crude product was dissolved in MeOH (0.5 mL) and the solution was heated at 40°C for 12 h. The solvent was evaporated under reduced pressure, the crude obtained was dissolved in DCM (0.1 mL). Et₂O (0.5 mL) was added and a precipitate was obtained. The solid was filtered and the filtrate was evaporated under reduced pressure to afford the title compound (23 mg).

HPLC/MS analysis (mobile phase: A/B from 70/30 to 45/55 in 10 min, from 45/55 to 10/90 in 5 min, 10/90 for 5 min, mass range 150-1000 amu): retention time :9.15 min, MS; m/z (ES): 1108 [MH]⁺.

¹H-NMR (500MHz) δ: 8.73 (s, 1H), 7.97 (d, 1H), 7.00 (d, 1H), 5.49 (bm, 1H), 4.70 (d, 1H), 4.35 (bm, 1H), 3.50 (m, 1H), 3.35 (m, 2H), 3.05 (m, 2H), 3.00 (m, 2H), 2.68□2.50 (m, 2H), 1.38 (m, 2H), 1.20 (m, 2H).

Example 46

4''-O-[3-[4-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]propionyl]-6-O-methyl-erythromycin A

To a solution of intermediate 68 (20 mg) in MeOH (1 mL), DIPEA (0.021 mL) and 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-1,4-dihydro-quinoline-3-carboxylic acid (40 mg) were added and the reaction mixture was heated at 40°C for 24 h. The solvent was evaporated and the residue dissolved in DCM (2 mL). Isocyanate polymer-bound (Aldrich, loading 2mmol/g, 120 mg) was added and the mixture was shaken at room temperature overnight. The resin was filtered and washed with DCM (2 mL), MeOH (2 mL) and DCM (2 mL). The collected organic extracts were evaporated under reduced pressure. The residue was dissolved in DCM (3 mL) and washed with water (3x3 mL), the combined aqueous phase was extracted with DCM (3x3 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 90/10) affording the title compound (7.8 mg).

¹H-NMR (500MHz) δ: 15.00 (bs, 1H), 8.79 (s, 1H), 8.04 (d, 1H), 7.35 (d, 1H), 4.72 (d, 1H), 4.35 (m, 1H), 3.55 (m, 1H), 3.40-3.10 (m, 2H), 2.86-2.64 (m, 6H), 2.60 (m, 4H), 1.39 (m, 2H), 1.15 (m, 2H).

Example 47

4''-O-[3-[4-(3-carboxy-1-ethyl-1,4-dihydro-6-fluoro-4-oxo-[1,8]naphthylridinyl)-1-piperazinyl]propionyl]-6-O-methylerythromycin A

To a solution of intermediate 68 (20 mg) in anhydrous MeOH (2 mL) 1-ethyl-6-fluoro-4-oxo-7-piperazin-1-yl-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid (19 mg) was added. The reaction mixture was stirred at 40°C overnight, the solvent was evaporated under reduced pressure and the residue dissolved in DCM (3 mL). Isocyanate polymer-bound (Aldrich, loading 2mmol/g, 118 mg) was added and the mixture was shaken at room temperature overnight. The resin was filtered and washed with DCM (3 mL), MeOH (3 mL) and DCM (3

mL). The collected organic extracts were evaporated under reduced pressure. The residue was dissolved in DCM (5 mL) and washed with water (3x3 mL), the combined aqueous phase was extracted with DCM (3x3 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent: DCM/MeOH 90/10) affording the title compound (12 mg).
¹H-NMR (500MHz) δ: 15.00 (bs, 1H), 8.71 (s, 1H), 8.12 (m, 1H), 4.72 (d, 1H), 4.41 (q, 2H), 4.35 (m, 1H), 3.85 (m, 4H), 2.84-2.54 (m, 4H), 2.64 (m, 4H), 1.51 (t, 3H).

Example 48

4"-O-[3-[4-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-1-piperazinyl]ethanoyl]-6-O-methyl-erythromycin A

To a solution of intermediate 70 (82 mg) in DMSO (0.5 mL), a preformed solution of DIPEA (0.054 mL) and 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-1,4-dihydro-quinoline-3-carboxylic acid (38 mg) in DMSO (1.3 mL) was added. The reaction mixture was stirred at room temperature for 6 h. Water (10 mL) and EtOAc (10 mL) were added and the aqueous phase was extracted with EtOAc (3x10 mL). The organic phase was dried, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 90/10) and heated in MeOH (12 mL) at 40°C for 16 h. Solvent evaporation under reduced pressure afforded the title compound (37 mg).
¹H-NMR (500MHz) δ: 15.00 (bs, 1H), 8.76 (s, 1H), 7.99 (d, 1H), 7.36 (d, 1H), 4.75 (d, 1H), 4.36 (m, 1H), 3.55 (m, 1H), 3.45-3.25 (d+d, 2H), 3.41 (m, 4H), 2.84 (m, 4H), 1.40-1.16 (m, 4H).

Example 49

4"-O-[2-[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]ethanoyl]-6-O-methyl-erythromycin A

To a solution of intermediate 70 (40 mg) in DMSO (0.3 mL), a preformed solution of DIPEA (0.036 mL) and intermediate 7 (23 mg) in DMSO (0.7 mL) was added. The reaction mixture was stirred at room temperature for 16 h. Water (5 mL) and EtOAc (10 mL) were added and the aqueous phase was extracted with EtOAc (3x10 mL). The organic phase was dried, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 90/10) and heated in MeOH (12 mL) at 50°C for 16 h. Solvent evaporation under reduced pressure afforded the title compound (11 mg).
¹H-NMR (500MHz) δ: 15.07 (bs, 1H), 8.74 (s, 1H), 8.05 (s, 1H), 7.55 (s, 1H), 5.30 (t, 1H), 4.75 (d, 1H), 3.55 (m, 1H), 3.41 (bm, 2H), 3.45-3.40 (m, 1H), 3.04-3.00 (m, 2H), 1.39-1.1 (m, 4H).

Example 50

4"-O-[2-[2-[(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]ethanoyl]-6-O-methyl-erythromycin A

To a solution of intermediate 70 (46 mg) in DMSO (0.3 mL), a preformed solution of DIPEA (0.036 mL) and intermediate 8 (24 mg) in DMSO (0.7 mL) was added. The reaction mixture was stirred at room temperature for 16 h. Water (5 mL) and EtOAc (10 mL) were added and the aqueous phase was extracted with EtOAc (3x10 mL). The organic phase was dried,

filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 90/10) and heated in MeOH (12 mL) at 50°C for 16 h. Solvent evaporation under reduced pressure afforded the title compound (10 mg).

¹H-NMR (500MHz) δ: 15.30 (bs, 1H), 8.70 (s, 1H), 7.94 (d, 1H), 7.01 (d, 1H), 5.51 (bm, 1H), 4.75 (d, 1H), 3.60 (d, 1H), 3.51 (m, 1H), 3.40 (d, 1H), 3.38 (m, 2H), 3.10-3.02 (m, 2H), 1.40-1.06 (m, 4H).

Example 51

4''-O-[3-[[2-[(3-carbamoyl-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A
and

4''-O-[3-[[2-[(3-carbamoyl-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A

A suspension of a 40/60 mixture of intermediates 19 and 20 (50 mg) in i-PrOH (1 mL) and DBU (0.64 mL) was heated at 50°C for 30 min in a sealed tube. Intermediate 69 (50 mg) was added and the reaction mixture was stirred at 70°C for 24 h then concentrated under reduced pressure. Water (10 mL) was added and the obtained mixture was extracted with EtOAc (3x10 mL). The combined organic phase was dried, filtered and concentrated under reduced pressure. The crude product was purified by preparative TLC (eluent DCM/MeOH/NH₄OH 90/10/2) and stirred in MeOH (10 mL) at 50°C overnight. Solvent evaporation under reduced pressure gave the title compound (13 mg).

¹H-NMR (500MHz) δ: 9.83 (bm, 1H), 8.77 (s, 1H), 7.97 (d, 1H), 6.96 (d, 1H), 5.68 (bm, 1H), 5.24 (bm, 1H), 4.70 (d, 1H), 4.36 (m, 1H), 3.47-3.30 (m, 3H), 3.04-2.80 (m, 4H), 2.65-2.52 (m, 4H); 1.35-1.12 (m, 4H).

Example 52

4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A

To a solution of example 38 (60 mg) in MeOH (20 mL), Pd/C (10%, 30 mg) was added and the mixture was hydrogenated at room temperature at 15 bar for 20 h. The catalyst was filtered and washed with MeOH and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (eluent DCM/MeOH/NH₃ 90/13/2) affording the title compound (23 mg).

MS; m/z (ES): 1089.6 [MH]⁺.

¹³C-NMR (75 MHz) δ: 177.9, 175.7, 172.3, 167.8, 147.0, 145.1, 133.2, 127.5, 122.2, 118.4, 107.3, 104.2, 102.0, 96.0, 80.4, 78.8, 78.3, 78.1, 74.3, 72.7, 71.1, 69.1, 67.8, 65.2, 63.0, 50.7, 49.5, 47.7, 45.3, 44.9, 44.5, 42.8, 40.3, 39.2, 38.8, 37.2, 35.4, 35.2, 34.5, 21.8, 21.2, 21.0, 19.7, 18.4, 18.0, 16.0, 12.4, 10.6, 9.1, 8.1.

Example 53

4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-propyl-erythromycin A

To a solution of intermediate 74 (200 mg) in i-PrOH (5 mL) intermediate 7 (150 mg) was added and the mixture was shaken at 80°C for 60 h. The solvent was evaporated, the residue

was triturated with DCM (2 mL). The solid was filtered, washed with DCM (1 mL) and the mother liquor was concentrated under reduced pressure. The crude product was precipitated from EtOAc / n-hexane 1/1 two times affording the title compound (8.3 mg).

MS; m/z (ES): 1152.3 [MH]⁺.

5 ¹³C-NMR (500 MHz) (δ/ppm): 177.9, 175.7, 172.3, 167.8, 147.0, 145.1, 133.2, 127.5, 122.2, 118.4, 107.3, 104.2, 102.0, 96.0, 80.4, 78.8, 78.3, 78.1, 74.3, 72.7, 71.1, 69.1, 67.8, 65.2, 63.0, 50.7, 49.5, 47.7, 45.3, 44.9, 44.5, 42.8, 40.3, 39.2, 38.8, 37.2, 35.4, 35.2, 34.5, 21.8, 21.2, 21.0, 19.7, 18.4, 18.0, 16.0, 12.4, 10.6, 9.1, 8.1.

10 Example 54

(11S, 11aR)-11-(carboxycyanomethyl)-4''-O-[3-[4-(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)piperazinyl]propionyl]-11-deoxy-6-O-methyl-erythromycin A

To a solution of intermediate 81 (10 mg) in anhydrous MeOH (0.5 mL), 1-cyclopropyl-1,4-dihydro-4-oxo-7-(piperazin-1-yl)-quinoline-3-carboxylic acid (18 mg) and DIPEA (0.010 mL) were added. The reaction mixture was stirred at 40°C overnight then the solvent was evaporated and the residue dissolved in DCM (2 mL). Isocyanate polymer-bound (Aldrich, loading 2mmol/g, 56 mg) was added and the mixture shaken at room temperature overnight. The resin was filtered and washed with DCM (2 mL), MeOH (2 mL) and DCM (2 mL). The collected organic extracts were evaporated under reduced pressure. The residue was dissolved in DCM (3 mL) and washed with water (3x3 mL), the combined aqueous phase was extracted with DCM (3x3 mL). The organic phase was dried, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 90/10) affording the title compound (9 mg).

25 ¹H-NMR (500MHz) δ: 15.36 (bs, 1H), 11.29 (mb, 1H), 8.77 (s, 1H), 8.32 (d, 1H), 7.20 (d, 1H), 7.14 (dd, 1H), 5.26 (dd, 1H), 4.98 (d, 1H), 4.73 (m, 2H), 4.65 (bm, 1H), 4.30 (bm, 1H), 3.88 (d, 1H), 3.80 (bm, 1H), 3.69-3.64 (m, 3H), 3.51 (m, 1H), 3.46 (m, 4H), 3.33 (s, 3H), 3.10 (m, 7H), 3.02 (m, 1H), 2.90 (m, 1H), 2.79 (m, 2H), 2.68 (m, 4H), 2.59 (m, 3H), 2.42 (d, 1H), 1.93 (m, 1H), 1.86 (m, 1H), 1.75 (m, 2H), 1.66 (m, 1H), 1.7-1.2 (m, 2H), 1.5 (s, 3H), 1.37 (m+s, 5H), 1.17 (s, 3H), 1.27-1.04 (m, 20H), 0.91 (t, 3H).

30 Example 55

(11S, 11aR)-11-(carboxycyanomethyl)-4''-O-[3-[4-(1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)piperazinyl]propionyl]-11-deoxy-6-O-methyl-erythromycin A

To a solution of intermediate 81 (10 mg) in anhydrous MeOH (0.5 mL), 1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo 7-(piperazin-1-yl)-quinoline (16 mg) and DIPEA (0.010 mL) were added. The reaction mixture was stirred at 40°C overnight, the solvent was evaporated and the residue dissolved in DCM (2 mL). Isocyanate polymer-bound (Aldrich, loading 2mmol/g, 0.056 g) was added and the mixture was shaken at room temperature overnight. The resin was filtered and washed with DCM (2 mL), MeOH (2 mL) and DCM (2 mL). The combined organic extracts were evaporated under reduced pressure. The residue was dissolved in DCM (3 mL) and washed with water (3x3 mL), the combined aqueous phase was extracted with DCM (3x3 mL). The organic phase was dried, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 90/10) affording the title compound (7 mg).

¹H-NMR (500MHz) δ : 7.99 (d, 1H), 7.62 (d, 1H), 7.26 (d, 1H), 6.16 (d, 1H), 5.26 (dd, 1H), 4.98 (d, 1H), 4.74 (d, 1H), 4.73 (d, 1H), 4.63 (d, 1H), 4.33 (m, 1H), 3.88 (d, 1H), 3.78 (m, 1H), 3.67 (d, 1H), 3.35 (m, 1H), 3.32 (s, 1H), 3.26 (m, 4H), 3.25 (m, 2H), 3.10 (s, 3H), 3.09 (s, 1H), 3.02 (m, 1H), 2.90 (m, 1H), 2.82-2.78 (m, 2H), 2.73-2.69 (m, 5H), 2.61-2.57 (m, 3H), 2.42 (m, 1H), 2.48 (s, 6H), 1.93 (m, 1H), 1.87 (m, 1H), 1.87-1.70 (m, 3H), 1.70-1.65 (m, 3H), 1.49 (s, 3H), 1.37 (s, 3H), 1.27 (d, 3H), 1.26 (m, 2H), 1.22 (d, 3H), 1.17 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H), 1.10 (s, 3H), 1.05 (m, 2H), 1.05 (d, 3H), 0.91 (t, 3H).

Example 56

(11S, 11aR)-11-(carboxycyanomethyl)-4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-11-deoxy-6-O-methyl-erythromycin A

To a solution of intermediate **81** (10 mg) in MeOH (1 mL) DIPEA (0.01 mL) and intermediate **8** (17 mg) were added. The reaction was stirred at 60°C for 3 days then cooled to room temperature and DCM (2 mL) and 4-benzyloxybenzaldehyde polymer-bound (Aldrich, loading 2.5-3mmol/g, 56 mg) were added. The reaction mixture was shaken at room temperature for 24 h. The resin was filtered and washed with DCM (2 mL), MeOH (2 mL) and DCM (2 mL). The combined organic extracts were evaporated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 90/10) affording the title compound (6 mg).

HPLC/MS analysis (mobile phase: A/B from 80/20 to 10/90 in 20 min, mass range 150-1000 amu): retention time :10.18 min, MS; m/z (ES): 1156 [MH]⁺.

Example 57

(11S, 11aR)-4"-O-[3-[4-(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)-piperazinyl]propionyl]-11-(carboxycyanomethyl)-11-deoxy-6-O-methyl-erythromycin A

To a solution of intermediate **81** (10 mg) in anhydrous MeOH (0.5 mL), 7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-(piperazin-1-yl)-quinoline-3-carboxylic acid (20 mg) and DIPEA (0.010 mL) were added. The reaction mixture was stirred at 60°C for 2 days, the solvent was evaporated and the residue dissolved in DCM (2 mL). Isocyanate polymer-bound (Aldrich, loading 2mmol/g, 56 mg) was added and the mixture was shaken at room temperature overnight. The resin was filtered and washed with DCM (2 mL), MeOH (2 mL) and DCM (2 mL). The combined organic extracts were evaporated under reduced pressure. The residue was dissolved in DCM (3 mL) and washed with water (3x3 mL) the combined aqueous phase was extracted with DCM (3x3 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 90/10) affording the title compound (10 mg).

¹H-NMR (500MHz) δ : 14.47 (bs, 1H), 8.82 (s, 1H), 8.03(d, 1H), 8.11 (d, 1H), 5.26 (dd, 1H), 4.98 (d, 1H), 4.74 (s, 1H), 4.73 (d, 1H), (4.63 (d, 1H), 4.32 (m, 1H), 3.87 (d, 1H), 3.78 (m, 1H), 3.67 (d, 1H), 3.57 (m, 1H), 3.33 (s, 3H), 3.28 (bm, 1H), 3.18 (bs, 1H), 3.10 (m+s, 3H + 1H), 3.02 (m, 1H), 2.91 (m, 1H), 2.80 (m, 2H), 2.71 (bm, 4H), 2.59 (m, 4H), 2.44 (s, 6H), 2.43 (d, 1H), 1.95-1.82 (m, 2H), 1.76-1.60 (m, 5H), 1.49 (s, 3H), 1.43 (m, 1H), 1.38 (s, 3H),

1.26 (s, 3H), 1.25 (m, 1H), 1.22 (d, 3H), 1.22 (m, 2H), 1.18 (d, 3H), 1.14 (d, 3H), 1.12 (d, 3H), 1.11 (d, 3H), 1.05 (d, 3H), 0.91 (t, 3H).

Example 58

5 (11*S*, 11*aR*)-4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-11-(carboxycyanomethyl)-11-deoxy-6-O-methyl-erythromycin A

A solution of intermediate 7 (54 mg) and DIPEA (0.030 mL) in anhydrous i-PrOH (2 mL) was left in ultrasonic bath for 1 min. Intermediate 81 (60 mg) was added and the reaction mixture was stirred at 120°C for 7 days. The solvent was evaporated, the residue dissolved in MeOH (3 mL) and the mixture stirred at room temperature overnight. After solvent evaporation, the residue was dissolved in DCM (3 mL), 4-benzyloxybenzaldehyde polymer-bound (Aldrich, loading 2.5-3mmol/g, 160 mg) was added and the mixture was shaken at room temperature overnight. The resin was filtered and washed with DCM (7 mL), MeOH (7 mL) and DCM (7 mL). The combined organic extracts were concentrated under reduced pressure. The residue was dissolved in DCM (10 mL) and washed with water (3x10 mL) and the combined aqueous phase was extracted with DCM (3x10 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 90/10) affording the title compound (29 mg).

¹H-NMR (500MHz) δ: 8.74 (s, 1H), 8.05 (s, 1H), 7.55 (s, 1H), 5.25 (m, 2H), 4.97 (d, 1H), 4.74 (d, 1H), 4.71 (d, 1H), 4.57 (d, 1H), 4.33 (m, 1H), 3.87 (d, 1H), 3.70 (m, 1H), 3.65 (d, 1H), 3.56 (m, 1H), 3.39 (m, 2H), 3.32 (s, 3H), 3.19 (dd, 1H), 3.09 (m+s, 4H), 3.02-2.95 (m, 5H), 2.90 (m, 1H), 2.61-2.53 (m, 4H), 2.42 (m, 4H), 2.31 (s, 6H), 1.92-1.58 (m, 7H), 1.49 (s, 3H), 1.43 (m, 2H), 1.36 (s, 3H), 1.86-1.26 (m, 6H), 1.19 (m, 1H), 1.13-1.11 (m, 9H), 1.04 (m, 3H), 0.91 (t, 3H).

Example 59

30 (11*S*, 11*aR*)-11-(carboxycyanomethyl)-4''-O-[3-[4-(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)piperazinyl]propionyl]-11-deoxy-6-O-methyl-erythromycin A

To a solution of intermediate 81 (40 mg) in anhydrous MeOH (2 mL), 1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-(piperazin-1-yl)-quinoline-3-carboxylic acid (82 mg) and DIPEA (0.038 mL) were added. The reaction mixture was stirred at 40°C overnight, the solvent was evaporated and the residue dissolved in DCM (4 mL). Isocyanate polymer-bound (Aldrich, loading 2mmol/g, 220 mg) was added and the reaction mixture was shaken at room temperature overnight. The resin was filtered and washed with DCM (4 mL), MeOH (4 mL) and DCM (4 mL). The combined organic extracts were evaporated under reduced pressure. The residue was dissolved in DCM (5 mL) and washed with water (3x3 mL), the combined aqueous phase was extracted with DCM (3x3 mL). The organic phase was dried, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 90/10) affording the title compound (19 mg).

¹H-NMR (500MHz) δ: 14.98 (bs, 1H), 8.80 (s, 1H), 8.05 (d, 1H), 8.03 (d, 1H), 7.35 (d, 1H), 5.26 (dd, 1H), 4.98 (d, 1H), 4.74 (m, 2H), 4.72 (d, 1H), 4.60 (d, 1H), 4.34 (m, 1H), 3.88 (d,

1H), 3.75 (m, 1H), 3.67 (d, 1H), 3.54 (m, 1H), 3.33 (s, 3H), 3.32 (m, 1H), 3.21 (m, 1H), 3.10 (m, 5H), 3.02 (m, 1H), 2.90 (m, 1H), 2.85-2.70 (m, 2H), 2.70 (m, 4H), 2.58 (m, 4H), 2.43 (d, 1H), 2.32 (s, 6H), 1.92 (m, 1H), 1.86 (m, 1H), 1.76 (m, 2H), 1.66 (m, 2H), 1.58 (m, 1H), 1.50 (s, 3H), 1.43 (m, 1H), 1.39 (m, 1H), 1.37 (s, 3H), 1.30 (m, 1H), 1.25 (d, 3H), 1.21 (d, 3H), 1.22 (m, 1H), 1.17 (s, 3H), 1.14 (d, 3H), 1.13 (d, 3H), 1.12 (d, 3H), 1.05 (d, 3H), 0.91 (t, 3H).

Example 60

(11*S*, 11*aR*)-11-(carboxycyanomethyl)-4''-O-[3-[rel-(4*aS*,7*aS*)-6-(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)]octahydro-1*H*-pyrrolo[3,4-*b*]pyridin-1-yl]propionyl]-11-deoxy-6-*O*-methyl-erythromycin A

To a solution of intermediate 81 (40 mg) in anhydrous MeOH (2 mL), 1-cyclopropyl-6-fluoro-8-methoxy-7-(octahydro-pyrrolo[3,4-*b*]pyridin-6-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (98 mg) and DIPEA (0.038 mL) were added. The reaction mixture was stirred at 40°C overnight, the solvent was evaporated and the residue dissolved in DCM (4 mL). Isocyanate polymer-bound (Aldrich, loading 2mmol/g, 220 mg) was added and the mixture was shaken at room temperature overnight. The resin was filtered and washed with DCM (4 mL), MeOH (4 mL) and DCM (4 mL). The collected organic extracts were evaporated under reduced pressure. The residue was dissolved in DCM (5 mL) and washed with water (3x3 mL), the combined aqueous phase was extracted with DCM (3x3 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 90/10) affording the title compound (44 mg).

¹H-NMR (500MHz) δ: 15.05 (bs, 1H), 8.78 (s, 1H), 7.81 (d, 1H), 5.26 (dd, 1H), 4.95 (d, 1H), 4.74 (s, 1H), 4.60 (d, 1H), 4.56 (d, 1H), 4.60 (d, 1H), 4.32 (m, 1H), 4.01 (d, 1H), 3.90 (m, 1H), 3.87 (d, 1H), 3.70 (m, 1H), 3.65 (m, 3H), 3.56 (m, 1H), 3.30 (s, 3H), 3.18 (m, 1H), 3.17 (m, 1H), 3.09 (m, 1H), 3.10 (m, 4H), 3.02 (m, 1H), 2.95 (m, 1H), 2.91 (m, 1H), 2.78 (m, 2H), 2.62 (m, 4H), 2.60 (m, 1H), 2.52 (m, 3H), 2.36 (d, 1H), 2.35 (m, 1H), 2.29 (s, 6H), 1.92 (m, 1H), 1.90 (m, 1H), 1.86 (m, 1H), 1.76 (m, 1H), 1.72-1.68 (m, 5H), 1.60 (m, 2H), 1.49 (s, 3H), 1.37 (s, 3H), 1.25 (d, 3H), 1.30 (m, 1H), 1.20 (m, 2H), 1.14-1.06 (m, 9H), 1.15 (s, 3H), 1.11 (d, 3H), 1.05 (d, 3H), 0.91 (t, 3H).

Example 61

(11*S*,11*aR*)-11-(carboxycyanomethyl)-4''-O-[3-[4-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridinyl)piperazinyl]propionyl]-11-deoxy-6-*O*-methyl-erythromycin A

To a solution of intermediate 81 (20 mg) in anhydrous MeOH (2 mL) 1,4-dihydro-1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-[1,8]naphthyridine-3-carboxylic acid (21 mg) was added. The reaction mixture was stirred at room temperature overnight, the solvent was evaporated and the residue dissolved in DCM (3 mL). Isocyanate polymer-bound (Aldrich, loading 2 mmol/g, 134 mg) was added and the mixture was shaken at room temperature overnight. The resin was filtered and washed with DCM (3 mL), MeOH (3 mL) and DCM (3 mL). The collected organic extracts were evaporated under reduced pressure. The residue was dissolved in DCM (5 mL) and washed with water (3x3 mL) the combined aqueous phase was extracted with DCM (3x3 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated

under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 90/10) affording the title compound (14 mg).

¹H-NMR (500MHz) δ: 15.00 (bs, 1H), 8.70 (s, 1H), 8.12 (d, 1H), 4.74 (d, 1H), 4.72 (d, 1H), 4.40 (q, 2H), 4.35 (m, 1H), 3.85 (m, 4H), 2.78 (m, 1H), 2.75 (m, 2H), 2.73 (m, 1H), 2.57 (m, 2H), 1.51 (t, 3H).

Example 62

(11S, 11aR)-11-(carboxycyanomethyl)-4''-O-[3-[[2-[(3-carboxy-1,4-dihydro-1-ethyl-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-11-deoxy-6-O-methyl-erythromycin A

A solution of intermediate 81 (100 mg) and intermediate 3 (93 mg) in MeOH (1 mL) was shaken at 70°C for 16 h. The solvent was evaporated and the residue triturated with DCM (2 mL). The solid was filtered and washed with DCM (1 mL). The mother liquor was concentrated under reduced pressure to give a crude product that was precipitated from EtOAc/n-hexane 1/1 two times affording the title compound (27 mg).

MS; m/z (ES): 1127.1 [MH]⁺.

Example 63

(11S, 11aR)-11-(carboxycyanomethyl)-4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-11-deoxy-6-O-methyl-erythromycin A

A solution of intermediate 81 (100 mg) and intermediate 4 (97 mg) in MeOH (1 mL) was shaken at 70°C for 22 h. The solvent was evaporated, the residue was triturated with DCM (2 mL). The solid was filtered and washed with DCM (1 mL). The mother liquor was concentrated under reduced pressure. The crude product was precipitated from EtOAc/n-hexane two times affording the title compound (23 mg).

MS; m/z (ES): 1138.8 [MH]⁺.

Example 64

4''-O-[3-[4-(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)-1-piperazinyl]propionyl]-roxithromycin

To a solution of intermediate 83 (40 mg) in anhydrous MeOH (2 mL), 1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-(piperazin-1-yl)-quinoline-3-carboxylic acid (50 mg) and DIPEA (0.050 mL) were added. The reaction mixture was stirred at 40°C overnight, the solvent was evaporated and the residue dissolved in DCM (4 mL). Isocyanate polymer-bound (Aldrich, loading 2mmol/g, 114 mg) was added and the mixture was shaken at room temperature overnight. The resin was filtered and washed with DCM (4 mL), MeOH (4 mL) and DCM (4 mL). The collected organic extracts were evaporated under reduced pressure. The residue was dissolved in DCM (5 mL) and washed with water (3x3 mL) the combined aqueous phase was extracted with DCM (3x3 mL). The organic phase was dried, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 90/10) affording the title compound (33 mg).

¹H-NMR (500MHz) δ: 15.00 (bs, 1H), 8.78 (s, 1H), 8.03 (d, 1H), 7.35 (d, 1H), 5.18 (dd, 2H), 4.70 (d, 1H), 4.38 (m, 1H), 3.75 (m, 2H), 3.56 (m, 3H), 3.42 (s, 3H), 3.32 (m, 4H), 2.86-2.74 (m, 2H), 2.70 (m, 2H), 2.59 (m, 2H), 1.40 (m, 2H), 1.20 (m, 2H).

Example 65**4''-O-[3-[4-(3-carboxy-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridinyl)piperazinyl]propionyl]-roxithromycin**

- 5 To a solution of intermediate 83 (20 mg) in anhydrous MeOH (2 mL), 1-ethyl-6-fluoro-4-oxo-7-piperazin-1-yl-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (21 mg) was added. The reaction mixture was stirred at 40°C overnight, the solvent was evaporated and the residue dissolved in DCM (3 mL). Isocyanate polymer-bound (Aldrich, loading 2mmol/g, 128 mg) was added and the mixture was shaken at room temperature overnight. The resin was filtered
- 10 and washed with DCM (3 mL), MeOH (3 mL) and DCM (3 mL). The collected organic extracts were evaporated under reduced pressure. The residue was dissolved in DCM (5 mL) and washed with water (3x3 mL). The organic phase was dried, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 90/10) affording the title compound (19 mg).
- 15 ¹H-NMR (500MHz) δ: 15.04 (bs, 1H), 8.70 (s, 1H), 8.12 (d, 1H), 5.18 (d+d, 2H), 4.72 (d, 1H), 4.41 (q, 2H), 4.38 (m, 1H), 3.85 (m, 4H), 3.75 (m, 2H), 3.57 (t, 2H), 3.42 (s, 3H), 2.81-2.54 (m, 6H), 1.51 (t, 3H).

Example 66**4''-O-[3-[4-(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-roxithromycin**

- 20 To a solution of intermediate 83 (20 mg) in anhydrous i-PrOH (0.5 mL), intermediate 7 (17 mg) and DIPEA (0.030 mL) were added. The reaction mixture was stirred at 120°C for 2 days, the solvent was evaporated and the residue dissolved in MeOH (3 mL) and stirred
- 25 overnight at room temperature. The solvent was evaporated and the residue dissolved in DCM (3 mL). 4-Benzyloxybenzaldehyde polymer-bound resin (Aldrich, loading 2.5-3mmol/g 65 mg) was added and the mixture was shaken at room temperature overnight. The resin was filtered and washed with DCM (3 mL), MeOH (3 mL) and DCM (3 mL). The collected organic extracts were evaporated under reduced pressure. The residue was dissolved in DCM
- 30 (5 mL) and washed with water (3x3 mL). The organic phase was dried, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 70/30) affording the title compound (9 mg).
- 35 ¹H-NMR (500MHz) δ: 8.74 (s, 1H), 8.05 (d, 1H), 7.55 (s, 1H), 5.27 (bm, 1H), 5.18 (d+d, 2H), 4.70 (d, 1H), 4.36 (m, 1H), 3.80-3.70 (m, 2H), 3.58-3.53 (m, 3H), 3.42 (s, 3H), 3.40 (m, 2H), 3.02 (m, 2H), 2.98-2.93 (m, 2H), 2.60 (m, 2H), 1.39 (m, 2H), 1.16 (m, 2H).

Example 67**4''-O-[3-[4-(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-roxithromycin**

- 40 A mixture of intermediate 8 (0.010 mL) in i-PrOH (2 mL) was left in a ultrasonic bath for 1 minute. Intermediate 83 (20 mg) was added and the reaction mixture was stirred for 6 days at 120°C. The solvent was evaporated under reduced pressure, the residue dissolved in MeOH (4 mL) and the mixture stirred at room temperature overnight. After solvent evaporation the residue was dissolved in DCM (3 mL) and 4-benzyloxybenzaldehyde polymer-bond (Aldrich,

loading 2.5-3mmol/g, 0.14 g) was added. The reaction mixture was shaken at room temperature overnight. The resin was filtered off and washed with DCM (3 mL), MeOH (3 mL), DCM (3 mL); the combined organic extracts were evaporated under reduced pressure. The residue was dissolved in DCM (5 mL) washed with water (3x3 mL). The collected aqueous phase was extracted with DCM (2x5 mL). The organic phase was dried, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent: DCM/MeOH 80/20) affording the title compound (7.5 mg).

¹H-NMR (500MHz) δ: 8.73 (s, 1H), 7.98 (d, 1H), 7.00 (d, 1H), 5.48 (bm, 1H), 5.18 (m, 2H), 4.70 (d, 1H), 4.38 (m, 1H), 3.80-3.68 (m, 2H), 3.58-3.46 (m, 3H), 3.42 (s, 3H), 3.42 (m, 2H), 3.05 (m, 2H), 2.98-2.90 (m, 2H), 2.65 (m, 2H), 2.59 (m, 2H), 1.38 (m, 2H), 1.15 (m, 2H).

Example 68

4''-O-[2-[[3-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)-amino]propyl]amino]ethanoyl]-6-O-methyl-erythromycin A

and

4''-O-[2-[[3-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)-amino]propyl]amino]ethanoyl]-6-O-methyl-erythromycin A

To a solution of intermediate 70 (100 mg) in anhydrous MeCN (1 mL), intermediates 13 and 14 (mixture, 33 mg) in DMSO (5 mL) were added. The reaction mixture was stirred at room temperature for 2 h and then at 60°C for 3 h. The reaction mixture was diluted with DCM (10 mL), washed with water (3x100 mL), the organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent: from DCM to MeOH: DCM 95:5). The compound obtained was diluted in MeOH (0.5 mL) and stirred at room temperature for 2 days. Solvent evaporation under reduced pressure gave the crude compound, which was purified by flash chromatography (eluent: from DCM to MeOH: NH₄OH 98:2) to give the title compound (2 mg, mixture of Cl/F derivatives 85/15).

¹H-NMR (500 MHz) for 4''-O-[2-[[3-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)-amino]propyl]amino]ethanoyl]-6-O-methyl-erythromycin A δ: 15.09 (bs, 1H), 8.74 (d, 1H), 8.03 (s, 1H), 7.54 (s, 1H), 5.72 (bm, 1H), 5.00 (d, 1H), 4.75 (d, 1H), 4.37 (m, 1H), 3.76 (m, 1H), 3.58-3.40 (m, 5H), 3.32 (s, -OCH₃), 3.05-2.90 (m, 2H), 2.45 (d, 1H), 2.00 (m, 2H), 1.70 (m, 1H), 1.40-1.12 (m, 10H).

¹H-NMR (500 MHz) for 4''-O-[2-[[3-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)-amino]propyl]amino]ethanoyl]-6-O-methyl-erythromycin A δ: 15.39 (bs, 1H), 8.73 (d, 1H), 7.96 (d, 1H), 6.91 (s, 1H), 6.24 (bm, 1H).

HPLC/MS analysis (mobile phase: A/B from 70/30 to 40/60 in 14 min, from 40/60 to 10/90 in 3 min, 10/90 for 8 min, mass range 150-1000 amu): retention time: 10.4 min (1108 [MH]⁺) and 11.33 min (1124 [MH]⁺).

Example 69

4''-O-[2-[[2-[(7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)-amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A

and

4''-O-[2-[[2-[(1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A

To a suspension of intermediate 84 (23 mg) in i-PrOH (1 mL), DBU (0.026 ml) was added and the reaction mixture was heated at 50°C for 30 min in a sealed tube. Intermediate 68 (50 mg) was added to the reaction mixture, the tube was sealed and the reaction mixture was stirred at 70°C for 24 h then concentrated under reduced pressure. The crude product was purified by preparative TLC (eluent: DCM/MeOH/NH₄OH 90/10/1.5) and then stirred in MeOH (10 mL) at 50°C for 16 h. Solvent evaporation under reduced pressure gave the title compound (22 mg, a 70/30 mixture of Cl/F derivatives).

¹H-NMR (500 MHz) for 4''-O-[2-[[2-[(7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)-amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A δ 7.90 (s, 1H), 7.58 (d, 1H), 7.56 (s, 1H), 6.16 (d, 1H), 4.99 (d, 1H), 4.91 (m, 1H), 4.70 (d, 1H), 4.35 (m, 1H), 3.76 (m, 1H), 3.39-3.331 (m, 3H), 3.31 (s, -OCH₃), 3.04-2.95 (m, 4H), 2.61-2.53 (m, 2H), 2.42 (m, 1H), 1.90 (m, 1H), 1.30-1.12 (m, 10H).

¹H-NMR (500 MHz) for 4''-O-[2-[[2-[(1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A δ 7.95 (d, 1H), 7.58 (d, 1H), 6.91 (d, 1H), 6.12 (d, 1H).

HPLC/MS analysis (mobile phase: A/B from 70/30 to 45/55 in 20 min, from 45/55 to 10/90 in 5 min, mass range 200-1300 amu): retention time: 17.82 min (1061 [MH]⁺) and 21.15 min (1078[MH]⁺).

Example 70

4''-O-[3-[acetyl-2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)-amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A

To a solution of example 38 (60 mg) in DCM (3 mL), NaHCO₃ (42.3 mg) and acetic anhydride (5 μL) were added. The reaction mixture was stirred for 30 min at room temperature. Water (20 mL) was added and the mixture was extracted with DCM (3x10). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 56 mg. The crude product (10 mg) was diluted in MeOH (3 mL) and stirred at room temperature for 2 days. Solvent evaporation under reduced pressure gave the crude compound, which was purified by flash chromatography (eluent: DCM/MeOH: 98/2) to give the title compound (9 mg).

HPLC/MS analysis (mobile phase: A/B from 70/30 to 45/55 in 20 min, 45/55 for 10 min, mass range 200-1200 amu): retention time: 24.2 min (1166 [MH]⁺).

Example 71

4''-O-(3-(2-(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino)ethyl)-methyl-amino)propionyl)-11,12-dideoxy-11,12-(ethylaminocarbonyloxy)-6-O-methylerythromycin A

To a solution of example 36 (0.065g) in chloroform (0.4 mL), was added formaldehyde (0.0159 mL) and formic acid (0.0143 mL). The solution was stirred at room temperature for 2 days. The solvent was then removed in vacuo and the residue subjected to flash chromatography. Evaporation of combined pure fractions afforded 20 mg of pale yellow solid.

FAB-MS m/z 1191 (MH^+ , 61%).

Example 72

5 4''-O-(3-{[2-(1-cyclopropyl-6-fluoro-3-methoxycarbonyl-4-oxo-1,4-dihydro-quinolin-7-ylamino)-ethyl]-amino}-propionyl)-11,12-dideoxy-6-O-methyl-11,12-(aminocarbonyloxy)-erythromycin A

To a solution of intermediate 57 (700 mg) in CH_3CN (15 ml), H_2O (2 ml) and Et_3N (0.5 ml) was added intermediate 85 (540 mg). The reaction mixture was stirred at 60°C for 18 h. DCM (40 mL) and a saturated solution of $NaHCO_3$ (30 mL) were added to the reaction mixture. 10 The aqueous phase was washed with DCM (30 mL). The combined organic layers were concentrated under reduced pressure and the residue was purified on silica gel using: DCM/MeOH/ NH_4OH 90/9/0.5 affording the title compound (669 mg).

MS; m/z (ES): 1147.0 [MH] $^+$.

15 1H -NMR (500MHz, characteristic peaks) δ : 8.50 (s, 1H), 7.92 (bs, 1H), 6.93 (bs, 1H), 5.81(s, 1H), 5.12 (dd, 2H), 4.97 (d, 1H), 4.70 (d, 1H), 4.54 (d, 1H), 4.35 (m, 1H), 3.91 (s, 3H), 3.81 (d, 1H), 3.68 (m, 2H), 3.61 (d, 1H), 3.31 (s, 1H), 3.18 (dd, 1H), 2.42 (d, 1H), 2.30 (s, 6H), 1.42 (s, 3H), 1.36 (s, 3H), 0.87 (t, 3H).

Example 73

20 4''-O-{3-[2-[(3-carboxymethyl-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl]amino]propionyl}-11,12-dideoxy-6-O-methyl-11,12-(aminocarbonyloxy)-erythromycin A

To a solution of intermediate 57 (500 mg) in CH_3CN (10 ml), H_2O (1 ml) and Et_3N (0.2 ml) was added intermediate 10 (410 mg) and the resulting mixture was heated at 70°C for 5 h.

25 The solvent was evaporated *in vacuo* and to the residue was added DCM (50 mL). The resulting suspension was filtered and DCM was evaporated *in vacuo*. The residue was purified on an SPE-column in gradient solvent system DCM/MeOH/ NH_4OH affording of the title compound (302 mg).

MS; m/z (ES): 1162.5 [MH] $^+$.

30 1H -NMR (500MHz, characteristic peaks) δ : 8.50 (s, 1H), 7.88 (s, 1H), 7.62 (s, 1H), 5.79(s, 1H), 5.10 (dd, 2H), 5.00 (t, 1H), 4.97 (d, 1H), 4.70 (d, 1H), 4.54 (d, 1H), 4.33 (m, 1H), 3.91 (s, 3H), 3.80 (d, 1H), 3.68 (m, 2H), 3.60 (d, 1H), 3.44-3.40 (m, 1H), 3.36 (m, 2H), 3.31 (s, 1H), 3.17 (dd, 1H), 2.99 (t, 2H), 2.94 (s, 6H), 2.89-2.84 (m, 1H), 1.41 (s, 3H), 1.18 (d, 2H).

Example 74

35 4''-O-{3-[2-[(3-carboxymethyl-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl]-methyl-amino]propionyl}-11,12-dideoxy-6-O-methyl-11,12-(aminocarbonyloxy)-erythromycin A

To a solution of example 73 (0.300 mg) in $CHCl_3$ (10 mL), formaldehyde (90 mL) and formic acid (60 mL) were added. This mixture was heated at 60°C over night (18 h). DCM (40 mL) and a saturated solution of $NaHCO_3$ (20 mL) were added to the reaction mixture. The aqueous phase was washed with DCM (2 x 30 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified on column chromatography on silica gel using: DCM/MeOH/ NH_4OH 90/5/0.5 affording the title compound (170 mg).

MS; m/z (ES): 1176.93 [MH]⁺.

Example 75

5 4''-O-(3-{[2-(3-carboxy-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethyl]-methyl-amino}-propionyl)-11,12-dideoxy-6-O-methyl-11,12-(aminocarbonyloxy)-erythromycin A

To a solution of example 113 (230 mg) in MeOH (50 mL), Pd/C 10% (40 mg) was added and the mixture was hydrogenated at room temperature at 5 bar for 3 h. The catalyst was filtered and washed with MeOH and the filtrate was concentrated under reduced pressure. The
10 residue was purified on an SPE-column in gradient solvent system DCM/MeOH/NH₄OH affording of the title compounds (156 mg).

MS; m/z (ES): 1128.9 [MH]⁺.

Example 76

15 4''-O-{3-[2-[(3-carboxy-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl)amino]propionyl}-11,12-dideoxy-6-O-methyl-11,12-[amino(methyl)carbonyloxy]-erythromycin A

To a solution of example 34 (500 mg) in MeOH (60 mL), Pd/C 10% (150 mg) was added and the mixture was hydrogenated at room temperature at 5 bar for 4 h. The catalyst was filtered
20 and washed with MeOH and the filtrate was concentrated under reduced pressure. The residue was crystallised from EtOAc-diisopropyl eter affording the title compound (309 mg).

MS; m/z (ES): 1128.72 [MH]⁺.

Example 77

25 4''-O-{3-[2-[(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl)methylamino]propionyl}-6-O-methyl-erythromycin A

To a solution of example 38 (300 mg) in CHCl₃ (6 mL), formaldehyde (40 mL, 35% solution) and formic acid (20 mL) were added. This mixture was heated at 60°C for 3 h. To the reaction mixture additional amounts of formaldehyde (20 mL) and formic acid (20 mL) were
30 added and the reaction mixture was heated at 60°C for 7 h. DCM (30 mL) and a saturated solution of NaHCO₃ (20 mL) were added to the reaction mixture. The aqueous phase was washed with DCM (15 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (eluent: DCM/MeOH/NH₄OH 90/5/0.5) affording the title compound (178 mg).

35 MS; m/z (ES): 1129.2 [MH]⁺.

Example 78

40 4''-O-{3-[2-[(3-carboxymethyl-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl)amino]propionyl}-6-O-methyl-erythromycin A

To a solution of intermediate 69 (500 mg) in CH₃CN (10 ml), MeOH (1 ml), H₂O (1 ml) and Et₃N (0.2 ml) was added intermediate 10 (420 mg) and the resulting mixture was heated at 60°C for 24 hours. The solvent was evaporated *in vacuo* and to the residue was added DCM (50 mL). The resulting suspension was filtered and DCM was evaporated *in vacuo*. The

residue was purified on an SPE-column in gradient solvent system DCM/MeOH/NH₄OH affording of the title compound (382 mg).

MS; m/z (ES): 1137.50 [MH]⁺.

5 **Example 79**

4''-{3-[(2-[(3-carboxy-1-methyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl)amino]propionyl}-6-O-methyl-erythromycin A

To solution of intermediate 69 (100 mg) in i-PrOH (2 mL), intermediate 87 (98 mg) was added and shaken at 80°C for 41 hours. The solvent was evaporated, and the residue was trituated with DCM (2 mL). The resulting suspension was filtered and washed with DCM (1 mL). The filtrate was concentrated *in vacuo*. The crude product was precipitated from EtOAc-n-hexane twice affording the title compound (25 mg).

MS (ES⁺) m/z: [MH]⁺ = 1063.8.

15 **Example 80**

4''-{3-[(2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]butyl)amino]propionyl}-6-O-methyl-erythromycin A

To solution of intermediate 69 (170 mg) in MeOH (2 mL), intermediate 9 (200 mg) was added and shaken at 70°C for 24 hours. The solvent was evaporated, and the residue was trituated with DCM (2 mL). The resulting suspension was filtered and washed with DCM (1 mL). The filtrate was concentrated *in vacuo*. The crude product was precipitated from EtOAc-n-hexane twice affording the title compound (65 mg).

MS (ES⁺) m/z: [MH]⁺ = 1117.8.

25 **Example 81**

4''-O-[(2-[(3-carboxy-1-ethyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl)methylamino]propionyl}-6-O-methyl-erythromycin A

To a solution of example 39 (170 mg) in chloroform (2 ml), a 36% solution of HCOH (0.0254 ml) and HCOOH (0.0250 ml) was added and the reaction mixture was shaken at 65 °C for 21 hours. The reaction mixture was evaporated yielding 190 mg of product, which was purified by column chromatography (SPE-column, gradient polarity: 100% DCM to DCM: MeOH: NH₃ = 90:9:1.5) yielding 105 mg of impure product. Precipitation from EtOAc:n-hexane yielded pure title compound (83 mg).

MS (ES⁺) m/z: [MH]⁺ = 1105.5.

35

Example 82

4''-O-[(2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl)methylamino]propionyl}-6-O-methyl-erythromycin A

To a solution of example 40 (150 mg) in chloroform (2 ml), a 36% solution of HCOH (0.021 ml) and HCOOH (0.019 ml) was added and the reaction mixture was shaken at 65 °C for 2 hours. The reaction mixture was evaporated yielding 150 mg of product, which was purified by column chromatography (SPE-column, gradient polarity: 100% DCM to DCM: MeOH: NH₃ = 90:9:1.5) yielding 90 mg of impure product. Precipitation from EtOAc:n-hexane yielded pure title compound (65 mg).

MS (ES+) m/z: [MH]⁺ = 1119.3.

Example 83

4''-O-{3-[(2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-

5 **quinoliny)amino]butyl)amino]propionyl}-6-O-methyl-8a-aza-8a-homoerythromycin A**

To a solution of intermediate 26 (100 mg) in i-PrOH (1 mL), intermediate 9 (116 mg) was added and shaken at 80°C for 19 hours. The solvent was evaporated, and the residue was triturated with DCM (2 mL). The resulting suspension was filtered and washed with DCM (1 mL). The filtrate was concentrated *in vacuo*. The crude product was precipitated from EtOAc-

10 n-hexane twice affording the title compound (57 mg).

MS (ES+) m/z: [MH]⁺ = 1132.3.

Example 84

4''-O-{3-[(2-[(3-carboxy-1-methyl-1,4-dihydro-4-oxo-7-

15 **quinoliny)amino]ethyl)amino]propionyl}-6-O-methyl-8a-aza-8a-homoerythromycin A**

To solution of intermediate 26 (100 mg) in i-PrOH (1 mL), intermediate 87 (96 mg) was added and shaken at 60°C for 43 hours. The solvent was evaporated, and the residue was triturated with DCM (2 mL). The resulting suspension was filtered and washed with DCM (1 mL). The filtrate was concentrated *in vacuo*. The crude product was precipitated from EtOAc-

20 n-hexane the residue purified on a SiO₂ SPE-column (eluent: from DCM 100% to DCM: MeOH: NH₄OH 85/13/2) giving the title compound (5 mg).

MS (ES+) m/z: [MH]⁺ = 1077.9.

Example 85

25 **11,12-(aminocarbonyloxy)-4''-O-{3-[(2-[(3-carboxy-1-ethyl-4-oxo-1,4-dihydro-7-**
quinoliny)amino]ethyl)amino]propionyl}-11,12-dideoxy-6-O-methyl-erythromycin A

To solution of intermediate 57 (100 mg) in CH₃CN (3 mL), intermediate 3 (96 mg) was added and shaken at 80°C for 72 hours. The solvent was evaporated, and the residue was triturated with EtOAc (5 mL). The resulting suspension was filtered and washed with EtOAc

30 (1 mL). The filtrate was concentrated *in vacuo*. The crude product was precipitated from EtOAc-n-hexane twice giving the title compound (25 mg).

MS (ES+) m/z: [MH]⁺ = 1102.8.

Example 86

35 **4''-O-{3-[(2-[(3-carboxy-1-ethyl-**
1,4-dihydro-4-oxo-7-quinoliny)amino]ethyl)amino]propionyl}-11,12-dideoxy-11,12-
(methylaminocarbonyloxy)-6-O-methyl-erythromycin A

To solution of intermediate 59 (57 mg) in MeOH (1 mL), intermediate 3 (67 mg) was added and shaken at 65°C for 24 hours. The solvent was evaporated, and the residue was triturated

40 with EtOAc (3 mL). The resulting suspension was filtered and washed with EtOAc (1 mL). The filtrate was concentrated *in vacuo*. The crude product was precipitated from EtOAc-n-hexane twice giving the title compound (17 mg).

MS (ES+) m/z: [MH]⁺ = 1116.7.

Example 87

4''-O-{3-[(2-[(3-carboxy-1-ethyl-1,4-dihydro-4-oxo-7-quinoliny)amino]ethyl)amino]propionyl}-11,12-dideoxy-11,12-(ethylaminocarbonyloxy)-6-O-methyl-erythromycin A

- 5 To solution of intermediate 64 (100 mg) in MeOH (1 mL), intermediate 3 (64 mg) was added and shaken at 65°C for 24 hours. The solvent was evaporated, and the residue was triturated with EtOAc (3 mL). The resulting suspension was filtered and washed with EtOAc (1 mL). The filtrate was concentrated *in vacuo*. The crude product was precipitated from EtOAc-n-hexane twice giving the title compound (42 mg).
- 10 MS (ES+) m/z: [MH]⁺ = 1130.7.

Example 88

11,12-(aminocarbonyloxy)-4''-O-{3-[(2-[(3-carboxy-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinoliny)amino]ethyl)amino]propionyl}-11,12-dideoxy-6-O-methyl-erythromycin A

- 15 The pH value of a solution of example 32 (150 mg) in MeOH (30 mL) was adjusted to 5.5 by 1N HCl, 10% Pd/C (75 mg) was added and the reaction mixture was hydrogenated at 10 bar pressure for 22 hours at room temperature. The solvent was evaporated, water was added and the pH was adjusted to 9.5 with 2N NaOH. The aqueous layer was extracted with DCM (3 x 30 mL), the organic layer dried over Na₂SO₄ and evaporated. The crude product was
- 20 precipitated from EtOAc-n-hexane giving the title compound (35 mg).
- MS (ES+) m/z: [MH]⁺ = 1114.8.

Example 89

11,12-(aminocarbonyloxy)-4''-O-{[(2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinoliny)amino]ethyl)methylamino]propionyl}-11,12-dideoxy-6-O-methyl-erythromycin A

- 25 To a solution of example 33 (100 mg) in chloroform (2 ml), 36% solution of HCHO (0.0136 ml) and HCOOH (0.0123 ml) was added and shaken at 65 °C for 20 hours. The reaction mixture was evaporated yielding 120 mg of a complex mixture. The residue was purified by
- 30 column chromatography (SPE-column, gradient polarity: 100% DCM to DCM: MeOH: NH₃ = 90:9:1.5) yielding 20 mg of impure product. Precipitation from EtOAc:n-hexane yielded pure title compound (7 mg).
- MS (ES+) m/z: [MH]⁺ = 1147.0.

Example 90

4''-O-[3-[(2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinoliny)amino]ethyl)amino]propionyl]-azithromycin

- To a suspension of intermediate 51 (100 mg) in methanol (3 mL), intermediate 4 (72 mg) was added. This mixture was heated at 60°C for 24 h. The solvent was evaporated and the
- 40 residue purified by flash chromatography (eluent: DCM/MeOH/NH₃ 90/9/1.5) affording the title compound (13 mg).
- MS; m/z (ES): [MH]⁺. 1090.3.

Example 91

4''-O-[3-[[2-[(3-carboxy-1-methyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-azithromycin

To a suspension of intermediate 51 (100 mg) in methanol (3 mL), intermediate 87 (65 mg) was added. This mixture was heated at 60°C for 24 h. The solvent was evaporated and the residue purified by flash chromatography (eluent: DCM/MeOH/NH₃ 90/9/1.5) affording the title compound (22 mg).

MS; m/z (ES): [MH]⁺. 1064.2.

Example 92

4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]butyl]amino]propionyl]-azithromycin

To a suspension of intermediate 51 (100 mg) in methanol (3 mL), intermediate 9 (78 mg) was added. This mixture was heated at 60°C for 24 h. The solvent was evaporated and the residue purified by flash chromatography (eluent: DCM/MeOH/NH₃ 90/9/1.5) affording the title compound (24 mg).

MS; m/z (ES): [MH]⁺. 1118.5.

Example 93

4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]-methyl-amino]propionyl]-azithromycin

To a suspension of example 28 (500 mg) in chloroform (15 mL), a 36% aqueous solution of formaldehyde (0.150 mL) and formic acid (0.11 mL) were added. This mixture was stirred at room temperature for 48 h. Saturated NaHCO₃ (20 mL) was then added. The layers were separated, and the aqueous layer was washed with CH₂Cl₂ (2x10 mL). The combined organic layers were dried and concentrated under reduced pressure. The residue was dissolved in EtOAc (10 mL) and the product precipitated by adding n-hexane (40mL) affording the title compound (370 mg).

MS; m/z (ES): [MH]⁺. 1138.6.

¹³C-NMR (75 MHz) δ: 178.8; 177.6; 171.8; 167.4; 145.8; 143.2; 132.5; 127.6; 126.4; 17.9; 107.6; 104.5; 102.4; 94.8; 83.3; 78.9; 77.9; 77.5; 74.3; 73.9; 73.6; 73.0; 71.0; 70.1; 67.8; 65.6; 62.9; 62.4; 55.4; 52.9; 49.5; 45.1; 42.3; 41.9; 41.3; 40.7; 40.4; 36.4; 35.3; 35.1; 32.7; 27.5; 26.8; 21.9; 21.8; 21.3; 21.3; 17.9; 16.2; 14.7; 11.3; 9.2; 8.1; 7.5.

Example 94

11,12-carbonate-4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)amino]ethyl]methyldamino]propionyl]-11,12-dideoxy-azithromycin

Example 26 (150 mg) was dissolved in CHCl₃ (10 mL), then formaldehyde (0.034 mL, 36 %) and formic acid (0.031 mL) were added and reaction mixture was stirred at 60 °C for 4 h. The solvent was removed under reduced pressure and the residue purified by silicagel column (eluent: CHCl₃-MeOH-NH₄OH = 6:1: 0.1) giving the title compound (47 mg).

MS; m/z (ES): 1147 [MH]⁺.

Example 95

11,12-carbonate-4''-O- [3- [[2- [(3-carboxy-1-cyclopropyl-1,4-dihydro-7-chloro-4-oxo-6-quinoliny] amino] ethyl] methylamino] propionyl] -11,12-dideoxy-azithromycin

Example 25 (910 mg) was dissolved in CHCl₃ (62 mL), then formaldehyde (0.05 mL, 36 %) and formic acid (0.045 mL) were added and reaction mixture was stirred at reflux temperature for 6 h. Solvent was evaporated and the residue purified by silicagel column (eluent: CHCl₃-MeOH-NH₄OH = 6:1:0.1) affording the title compound (390 mg).

MS; m/z (ES): 1164.6 [MH]⁺.

Example 96

10 **11,12-carbonate-4''-O- [3- [[2- [(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinoliny] amino] ethyl] methylamino] propionyl] -11,12-dideoxy-azithromycin**

Example 95 (500 mg) was dissolved in MeOH (70 mL), Pd/C (300 mg, 10 %) was added and hydrogenation was performed at 3 x 10⁵ Pa for 4 h. The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The crude product was precipitated from DCM / n-hexane affording the title compound (350 mg).

MS; m/z (ES): 1130 [MH]⁺.

Example 97

20 **11,12-carbonate-4''-O- [3- [[2- [(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinoliny] amino] ethyl] amino] propionyl] -11,12-dideoxy-azithromycin**

Example 25 (100 mg) was dissolved in MeOH (8 mL), Pd/C (60 mg, 10 %) was added and hydrogenation was performed at 4 x 10⁵ Pa for 3 h. The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was purified by silicagel column [eluent: DMC-(MeOH-NH₄OH = 9:1.5)= 90:15] affording the title compound (32 mg).

MS; m/z (ES): 1116 [MH]⁺.

Example 98

30 **11,12-carbonate-4''-O- [3- [[2- [(3-carboxy-1-ethyl-1,4-dihydro-4-oxo-7-quinoliny] amino] ethyl] amino] propionyl] -11,12-dideoxy-azithromycin**

To solution of intermediate 50 (200 mg) in MeOH (2 mL), intermediate 3 (200 mg) was added and reaction mixture stirred at 65 °C for 24 h. After evaporation of the solvent, the residue was suspended in DCM, filtered off and the filtrate was evaporated to give the crude product (160 mg). The residue was purified by silicagel column (CHCl₃-MeOH-NH₄OH = 6:1:0.1). After crystallisation from EtOAc/n-hexane the title compound was obtained (50 mg).

MS; m/z (ES): 1104 [MH]⁺.

Example 99

40 **4''-O-[3-[2-[3-carboxy-6-fluoro-8-methoxy-1-cyclopropyl-4-oxo-1,4-dihydro-7-(quinoliny]amino]ethyl)amino]propionyl]-azithromycin**

To a suspension of intermediate 51 (500 mg) in acetonitrile (12 ml), intermediate 88 (417 mg), 0.5 ml of water and 0.25 ml of DBU were added. This mixture was heated at 85°C and stirred for 24h. The solvent was evaporated under reduced pressure and residue was purified

on SiO₂ SPE-column (eluent: from DCM 100% to DCM/MeOH/NH₄OH = 85/13/12) affording the title product.

MS; m/z (ES): 1139.6 [MH]⁺.

5 **Example 100**

4''-O-{3-[(2-[3-carboxy-6-fluoro-8-methoxy-1-cyclopropyl-4-oxo-1,4-dihydro-7-(quinolinyl)amino]ethyl)amino]propionyl}-6-O-methyl-erythromycin

10 To the suspension of intermediate 69 in acetonitrile (6 ml), intermediate 88 (230 mg), 0.25 ml of water and 0.08 ml of triethylamine were added. This mixture was heated at 85°C and stirred for 48h. The solvent was evaporated under reduced pressure and residue was purified on SiO₂ SPE-column (eluent: from DCM 100% to DCM/MeOH/NH₄OH = 85/13/12) affording the title product.

MS; m/z (ES): 1138.6 [MH]⁺.

15 **Example 101**

4''-O-(3-{[2-(7-chloro-1-cyclopropyl-3-methoxycarbonyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethyl]-amino}-propionyl)-azithromycin

20 To a solution of intermediate 51 (300 mg) in MeOH (5 ml) was added intermediate 10 (376 mg) and the resulting mixture was heated at 60°C for 24 hours. The solvent was evaporated *in vacuo* and to the residue was added DCM (50 mL). The resulting suspension was filtered and DCM was evaporated *in vacuo*. The residue was purified on an SPE-column in gradient solvent system DCM/MeOH/NH₄OH affording the title compound (99 mg).

MS; m/z (ES): 1138.06 [MH]⁺.

25 ¹H-NMR (selected peaks, 500MHz) δ 8.50 (s, 1H), 7.87 (s, 1H), 7.58 (s, 1H), 5.19 (d, 1H), 5.08 (t, 1H), 4.89 (m, 1H), 4.71 (d+ m, 2H), 4.56 (d, 1H), 4.41 (m, 1H), 4.26 (m, 1H), 3.91 (s, 3H), 3.78 (m, 1H), 3.68 (m, 1H), 3.61 (d, 1H), 3.43 (m, 1H), 3.38 (m, 2H), 3.31 (s, 3H), 3.01 (t, 2H), 2.75 (m, 1H).

Example 102

30 **4''-O-(3-{[2-(7-chloro-1-cyclopropyl-3-methoxycarbonyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethyl]-methyl-amino}-propionyl)-azithromycin**

35 To a solution of example 101 (150 mg) in CHCl₃ (6 mL), formaldehyde (90 mL) and formic acid (60 mL) were added. This mixture was heated at 60°C for 3 h. To the reaction mixture DCM (40 mL) and a saturated solution of NaHCO₃ (20 mL) were added. The aqueous phase was washed with DCM (15 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified on column chromatography on silica gel using: DCM/MeOH/NH₄OH 90/5/0.5 affording the title compound (90 mg).

MS; m/z (ES): 1152.47 [MH]⁺.

40 ¹H-NMR (selected peaks, 500MHz) δ 8.50 (s, 1H), 7.89 (s, 1H), 7.60 (s, 1H), 5.19 (d, 1H), 5.12 (t, 1H), 4.82 (m, 1H), 4.72 (d, 1H), 4.71 (m, 1H), 4.57 (d, 1H), 4.41 (m, 1H), 4.27 (m, 1H), 3.91 (s, 3H), 3.63 (d, 1H), 3.43 (m, 1H), 3.32 (s, 3H), 2.39 (d, 1H), 2.32 (s, 6H), 2.27 (s, 3H), 1.76 (d, 1H), 1.64 (dd, 1H), 1.50-1.44 (m, 1H), 0.90 (d, 3H), 0.88 (t, 3H).

Example 103

4''-O-(3-{[2-(1-cyclopropyl-3-methoxycarbonyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethyl]-amino}-propionyl)-azithromycin

To a solution of example 101 (150 mg) in MeOH (30 mL), Pd/C 10% (40 mg) was added and the mixture was hydrogenated at room temperature at 5 bar for 3.5 h. The catalyst was filtered and washed with MeOH and the filtrate was concentrated under reduced pressure. The residue was purified on an SPE-column in gradient solvent system DCM/MeOH/NH₄OH affording the title compound (90 mg).

MS; m/z (ES): 1105.0 [MH]⁺.

Example 104

4''-O-{3-[2-(1-cyclopropyl-6-fluoro-3-methoxycarbonyl-4-oxo-1,4-dihydro-quinolin-7-ylamino)-ethylamino]-propionyl}-azithromycin

To a solution of intermediate 51 (580 mg) in MeOH (14 ml) and H₂O (1 ml) was added intermediate 85 (550 mg). The reaction mixture was stirred at 60°C for 18 h. The solvent was concentrated under reduced pressure and the residue was purified on an SPE-column in gradient solvent system DCM/MeOH/NH₄OH affording the title compound (180 mg).

MS; m/z (ES): 1122.44 [MH]⁺.

Example 105

4''-O-{3-[2-[(3-carboxy-1-ethyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl}-azithromycin

To solution of intermediate 51 (300 mg) in i-PrOH (3 mL), intermediate 3 (205 mg) was added and shaken at 65°C for 4 days. The solvent was evaporated, and the residue was triturated with EtOAc (2 mL). The resulting suspension was filtered and washed with EtOAc (1 mL). The filtrate was concentrated *in vacuo*. The crude product was precipitated from EtOAc-n-hexane affording the title compound (250 mg).

MS (ES⁺) m/z: [MH]⁺ = 1078.9.

Example 106

4''-O-{3-[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl}-azithromycin

The pH value of a solution of example 28 (138 mg) in MeOH (30 mL) was adjusted to 5.5 by 1N HCl, 10% Pd/C (70 mg) was added and the reaction mixture was hydrogenated at 10 bar pressure for 18 hours at room temperature. The solvent was evaporated, water was added and the pH was adjusted to 9.5 with 2N NaOH. The aqueous layer was extracted with DCM (3 x 30 mL), the organic layer dried over Na₂SO₄ and evaporated. The crude product was purified by a silica gel SPE-column (eluent: from DCM 100% to DCM/MeOH/NH₄OH 90/9/1.5) and then precipitated from EtOAc:n-hexane giving the title compound (15 mg).

MS (ES⁺) m/z: [MH]⁺ = 1090.9.

Example 107

4''-O-{3-[2-[(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl}-azithromycin

To a solution of intermediate 51 (100 mg) in i-PrOH (3 mL), intermediate 8 (114 mg), triethylamine (0.200 mL) and water (0.200 mL) were added and shaken at 65 °C for 24 hours. The solvent was evaporated, and the residue was triturated with EtOAc (3 mL). The resulting suspension was filtered and washed with EtOAc (1 mL). The filtrate was concentrated *in vacuo*. The crude product was precipitated from EtOAc:n-hexane twice giving the title compound (20 mg).

MS (ES+) m/z: [MH]⁺ = 1122.7.

Example 108

10 4''-O-{3-[(2-[(3-carboxy-1-ethyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl)methylamino]propionyl}-azithromycin

To a solution of example 105 (250 mg) in chloroform (3 ml), a 36% solution of HCOH (0.036 ml) and HCOOH (0.032 ml) was added and shaken at 60 °C for 18 hours. The reaction mixture was evaporated and the residue purified by column chromatography (SPE-column, gradient polarity: 100% DCM to DCM: MeOH: NH₃ = 90:9:1.5) yielding 80 mg of pure product. Precipitation from EtOAc:n-hexane yielded title compound (30 mg).

MS (ES+) m/z: [MH]⁺ = 1092.8.

Example 109

20 4''-O-{3-[(2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl)methylamino]propionyl}-azithromycin

To a solution of example 90 (70 mg) in chloroform (3 ml), a 36% solution of HCHO (0.011 ml) and HCOOH (0.009 ml) was added and shaken at 60 °C for 7 hours. The reaction mixture was evaporated and the residue purified by column chromatography (SPE-column, gradient polarity: 100% DCM to DCM: MeOH: NH₃ = 90:9:1.5) yielding 45 mg of unpure product. Precipitation from EtOAc:n-hexane yielded pure title compound (23 mg).

MS (ES+) m/z: [MH]⁺ = 1105.2.

Example 110

30 4''-O-{3-[(2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl)methylamino]propionyl}-azithromycin

To a solution of example 93 (0.53 g) in MeOH (50 ml), 10% Pd/C (0.19 g) was added and shaken in Parr apparatus at 5 bars at r.t. for 3 hours. The catalyst was filtered, the solvent evaporated and the residue precipitated from EtOAc:n-hexane yielding 0.5 g of crude product. Purification by column chromatography (SPE-column, gradient polarity: 100% DCM to DCM: MeOH:NH₃ = 90:9:1.5) yielded 0.2 g product which was precipitated from EtOAc:n-hexane yielding pure title compound (0.13 g).

MS (ES+) m/z: [MH]⁺ = 1104.4.

Example 111

40 4''-O-{3-[(2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)amino]ethyl)methylamino]propionyl}-azithromycin

To a solution of example 107 (150 mg) in chloroform (3 ml), a 36% solution of HCHO (0.022 ml) and HCOOH (0.020 ml) was added and shaken at 60 °C for 17 hours. The reaction

mixture was evaporated and the residue purified by column chromatography (SPE-column, gradient polarity: 100% DCM to DCM: MeOH: NH₃ = 90:9:1.5) yielding 85 mg of impure product. Precipitation from EtOAc:n-hexane yielded pure title compound (30 mg).

MS (ES⁺) m/z: [MH]⁺ = 1123.0.

5

Example 112

4''-O-[3-[(2-[(3-carboxy-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-7-quinolinyl)amino]ethyl)amino]propionyl]-11,12-dideoxy-6-O-methyl-11,12-(methylaminocarbonyloxy)-erythromycin A

10 To a solution of intermediate 59 (600 mg) in acetonitrile (15 ml) was added intermediate 8 (310 mg) and the resulting mixture was heated at 80 °C for 22 hours. The solvent was evaporated *in vacuo*, MeOH (50 mL) was added to the residue and the mixture was heated at 60°C for 18 hours. The reaction suspension was filtered and the solvent was evaporated *in vacuo*. The resulting residue was dissolved in EtOAc (30 ml) and filtered. The residue was
15 crystallised twice from EtOAc-diisopropylether affording the title compound (167 mg).

MS; m/z (ES): 1146.48 [MH]⁺.

Example 113

20 11,12-(aminocarbonyloxy)-4''-O-(3-{[2-(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethyl]-methyl-amino}-propionyl)-11,12-dideoxy-6-O-methyl-erythromycin A

To a solution of example 32 (100 mg) in chloroform (1.5 mL) at room temperature HCHO (13 µL) and HCOOH (12.1 µL) were added and the mixture was stirred at 60 °C for 20 hours. The solvent was evaporated under reduced pressure, and the residue was dissolved in EtOAc
25 (30 ml) and extracted with 10% aqueous solution of NaHCO₃ (30 ml). The organic layer was concentrated under reduced pressure. The residue was precipitated from ethyl acetate / diisopropyl ether yielding the title compound (68 mg).

MS; m/z (ES): 1162.8 [MH]⁺.

30 Example 114

4''-O-[3-[(2-[(3-carboxy-7-chloro-1-ethyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl)amino]propionyl]-6-O-methyl-erythromycin A

To a solution of intermediate 69 (100 mg) in 5 ml 2-PrOH, intermediate 5 (77 mg) was added and stirred at 80°C for 9 days. The reaction was not complete so water (0.5 ml) was added
35 and stirring continued. After a further 3 hours the reaction was still not complete so 0.1 ml of triethylamine was added and stirring continued for 3 days at 90°C. MS showed that the reaction was then complete. The reaction mixture was evaporated and the residue dissolved in EtOAc and filtered. The dissolved residue was precipitated with n-hexane to give the title compound (91 mg).

40 MS; m/z (ES): 1111.5 [MH]⁺.

Example 115

4"-O-[3-[[2-[(3-carboxy-7-chloro-1-ethyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-azithromycin

- To a solution of intermediate 51 (100 mg) in 5 ml 2-PrOH, intermediate 5 (77 mg) was added and stirred at 80°C for 9 days. The reaction was not complete so water (0.5 ml) was added and stirring continued. After a further 3 hours the reaction was still not complete so 0.1 ml of triethylamine was added and stirring continued for 3 days at 90°C. MS showed that the reaction was then complete. The reaction mixture was evaporated and the residue dissolved in EtOAc and filtered. The dissolved residue was precipitated with n-hexane to give the title compound (89 mg).
- MS; m/z (ES): 1112.5 [MH]⁺.

Example 116

4"-O-[3-[[2-[(3-carboxy-1-ethyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A

- Example 114 (50 mg) was dissolved in 25 ml methanol and catalyst (10% Pd/C, 25mg) was added. The pH was adjusted to 6.0 and the mixture was shaken under hydrogen (5 bar) overnight. MS showed no starting material. The mixture was filtered, the pH was adjusted to 8.9 and the solvent was evaporated. The residue was dissolved in DCM (100 ml) and washed with NaHCO₃ (aq). The DCM was evaporated and 38 mg of crude product was obtained. After SPE (1 g) purification, the title compound (13 mg) was obtained. MS; m/z (ES): 1077.8 [MH]⁺.

Example 117

4"-O-[3-[[2-[(3-carboxy-1-ethyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-azithromycin

- Example 115 (50 mg) was dissolved in 25 ml of methanol and catalyst (10% Pd/C, 25mg) was added. The pH was adjusted to 6.0 and the mixture was shaken under hydrogen (5 bar) overnight. MS showed no starting material. The mixture was filtered, the pH was adjusted to 8.9 and the solvent was evaporated. The residue was dissolved in DCM (100 ml) and washed with NaHCO₃ (aq). The DCM was evaporated and 36 mg of crude product was obtained. After SPE (1 g) purification, the title compound (9 mg) was obtained. MS; m/z (ES): 1078.8 [MH]⁺.

Example 118

4"-O-[3-[[2-[(1-benzyl-3-carboxy-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-O-ethyl-8a-aza-8a-homoerythromycin A

- To a solution of intermediate 30 (100 mg) in i-PrOH (5 mL) was added intermediate 2 (70 mg). The resulting mixture was stirred at 80°C for 10 days. The solvent was evaporated under reduced pressure, MeOH (3 mL) was added, stirred at 80°C for 3 h, evaporated and the crude product was purified by flash chromatography (eluent: MeOH/DCM/NH₄OH 9/90/1.5) affording the title compound (5 mg). MS; m/z (ES): 1168.8 [MH]⁺.

Example 119**4"-O-[3-[(2-[(1-benzyl-3-carboxy-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl)amino]propionyl]-6-O-propyl-8a-aza-8a-homoerythromycin A**

To a solution of intermediate 35 (100 mg) in i-PrOH (5 mL) was added intermediate 2 (70 mg). The resulting mixture was stirred at 80°C for 10 days. The solvent was evaporated under reduced pressure, MeOH (3 mL) was added, stirred at 80°C for 3 h, evaporated and the crude product was purified by flash chromatography (eluent: MeOH/DCM/NH₄OH 9/90/1.5) affording the title compound (6 mg).

MS; m/z (ES): 1182.5 [MH]⁺.

Biological Data

The MIC (µg/ml) of test compounds against various organisms was determined including:

S. aureus Smith ATCC 13709, *S. pneumoniae* SP030, *S. pyogenes* 3565, *E. faecalis* ATCC 29212, *H. influenzae* ATCC 49247, and *M. catarrhalis* ATCC 23246.

Examples 1-4, 6-8, 10-11, 13-15, 21-26, 28-39, 41-50, 53-63, 66-81, 85-91, 93, 95-97, 99-101, 104-107 and 109-115 have an MIC ≤1 µg/ml against *S. aureus* Smith ATCC 13709, *S. pneumoniae* SP030, *S. pyogenes* 3565 and *E. faecalis* ATCC 29212.

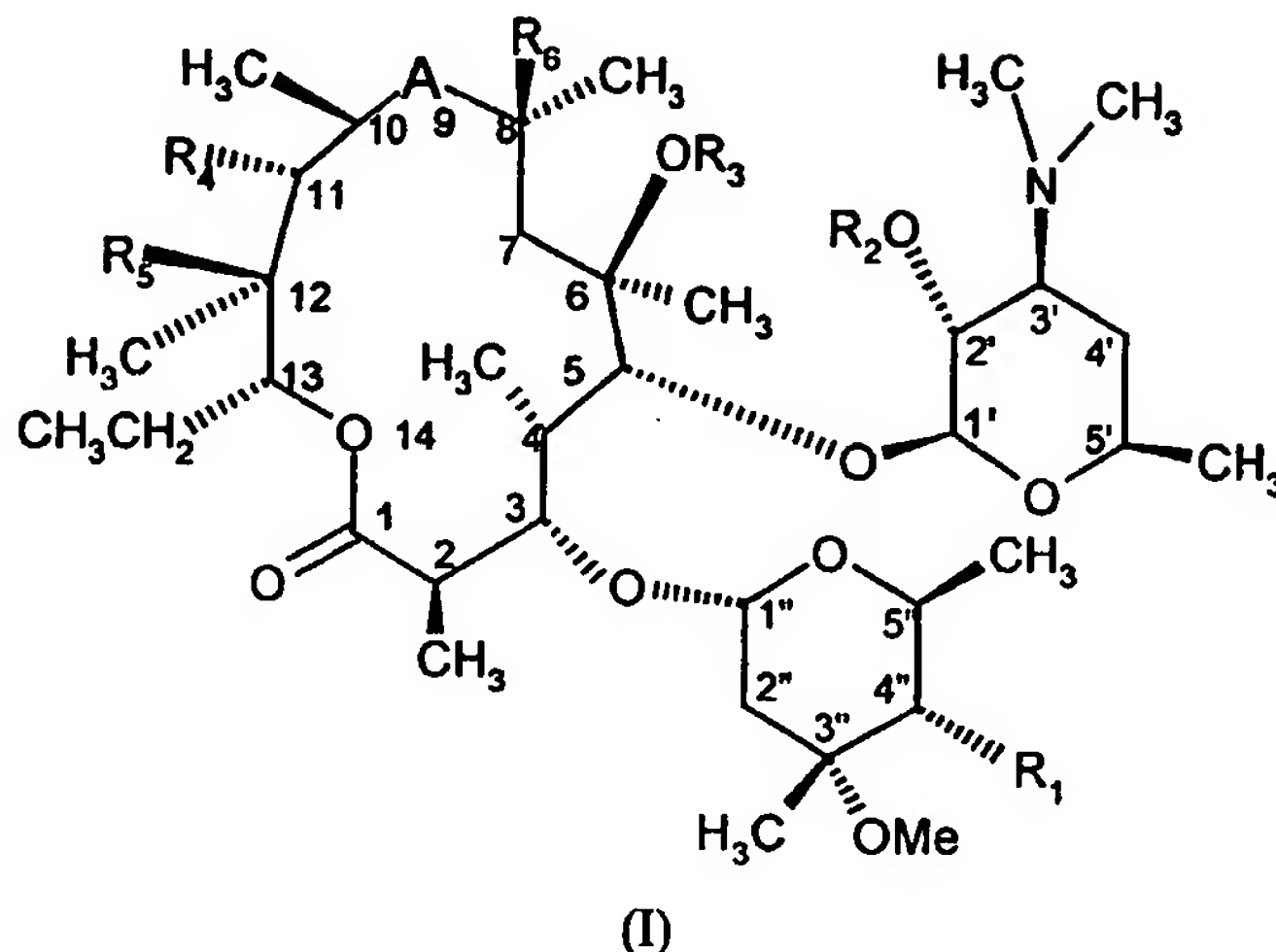
Examples 3, 6-7, 17, 25, 28, 32, 34, 36, 38-42, 45, 52-53, 75-76, 78, 81-82, 88, 93, 95-111 and 114-116 have an MIC ≤2 µg/ml against *H. influenzae* ATCC 49247 and *M. catarrhalis* ATCC 23246.

Examples 1-5, 11-15, 17-18, 20, 25-28, 32-36, 38-42, 45, 49-53, 56, 58, 62-63, 71, 73-74, 76, 78, 81-82, 85-88, 90-93, 95-97, 99-101, 107, 109 and 112-113 have an MIC <0.25 µg/ml against erythromycin resistant strains of *Streptococcus pneumoniae* and *Streptococcus pyogenes*.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims

1. A compound of formula (I)



wherein

A is a bivalent radical selected from:

- C(O)-, -C(O)NH-, -NHC(O)-, -N(CH₃)-CH₂-, -CH₂-N(CH₃)- or
 -C(NOCH₂OCH₂CH₂OCH₃)-;

R₁ is OC(O)(CH₂)_nXR₇;

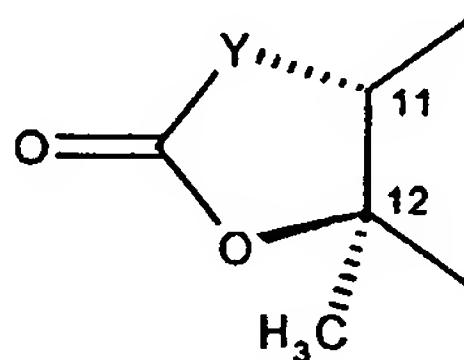
R₂ is hydrogen or a hydroxyl protecting group;

R₃ is hydrogen, C₁₋₄alkyl or C₃₋₆alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl;

- R₄ is hydroxy or C₃₋₆alkenyloxy optionally substituted by 9 to 10 membered fused bicyclic heteroaryl;

R₅ is hydroxy or

R₄ and R₅ taken together with the intervening atoms form a cyclic group having the following structure:

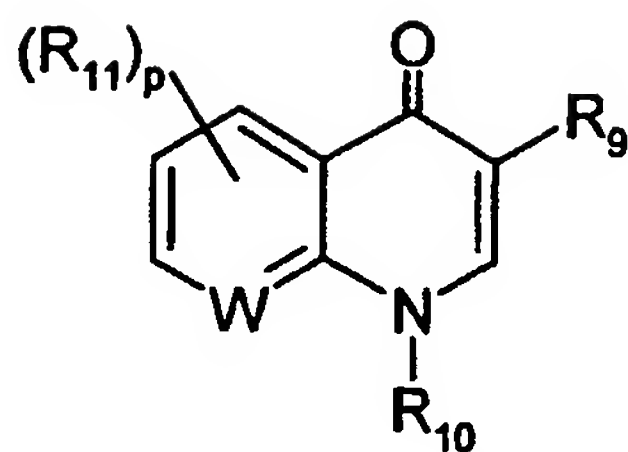


wherein Y is a bivalent radical selected from:

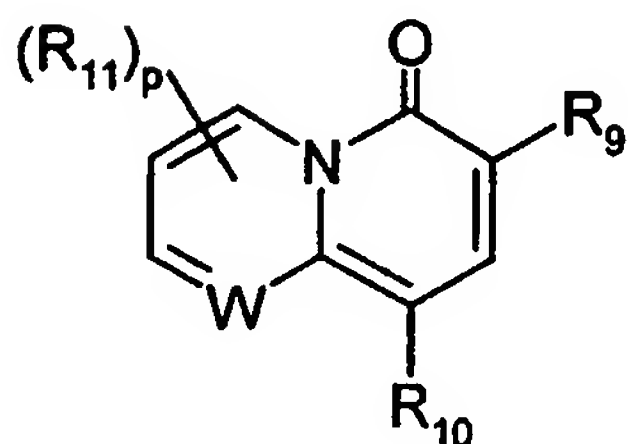
-CH₂-, -CH(CN)-, -O-, -N(R₈)- and -CH(SR₈)-;

R₆ is hydrogen or fluorine;

R₇ is a heterocyclic group having the following structures:



or



R_8 is hydrogen or

5 C_{1-4} alkyl substituted by a group selected from:

optionally substituted phenyl,

optionally substituted 5 or 6 membered heteroaryl,

optionally substituted 9 to 10 membered fused bicyclic heteroaryl;

R_9 is hydrogen, $C(O)OR_{12}$, $C(O)NHR_{12}$ or $C(O)CH_2NO_2$;

10 R_{10} is hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, optionally substituted phenyl or benzyl;

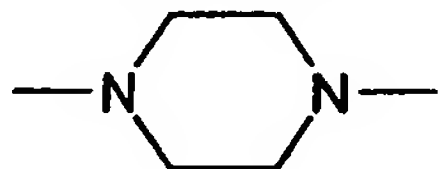
R_{11} is halogen, C_{1-4} alkyl, C_{1-4} thioalkyl, C_{1-4} alkoxy, NH_2 , $NH(C_{1-4}alkyl)$ or $N(C_{1-4}alkyl)_2$;

R_{12} is hydrogen or C_{1-4} alkyl;

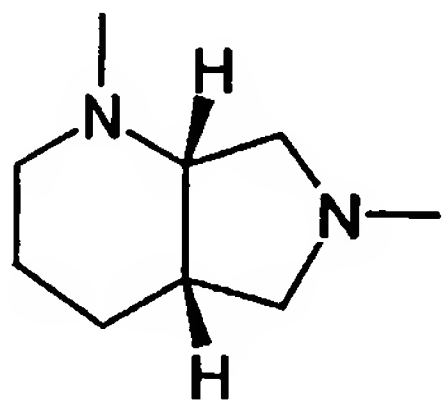
R_{13} is hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, optionally substituted phenyl or benzyl, acetyl or benzoyl;

15

X is $-U(CH_2)_mZ-$ or X is a group selected from:



or



20 U and Z independently are a divalent radical selected from:

$-N(R_{13})-$, $-O-$, $-S(O)_q-$, $-N(R_{13})C(O)-$, $-C(O)N(R_{13})-$, $-N[C(O)R_{13}]-$,

W is a carbon or a nitrogen atom;

n is 0 or an integer from 1 to 5;

m is an integer from 2 to 8;

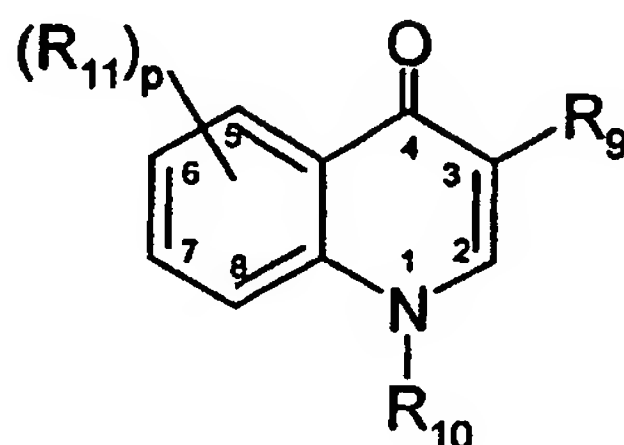
25 p is 0, 1 or 2;

q is 0, 1 or 2;

and pharmaceutically acceptable salts and solvates thereof.

2. A compound according to claim 1 wherein X is $\text{NH}(\text{CH}_2)_2\text{NH}$.
3. A compound according to claim 1 or 2 wherein R_7 is a heterocyclic group having the following structure:

5



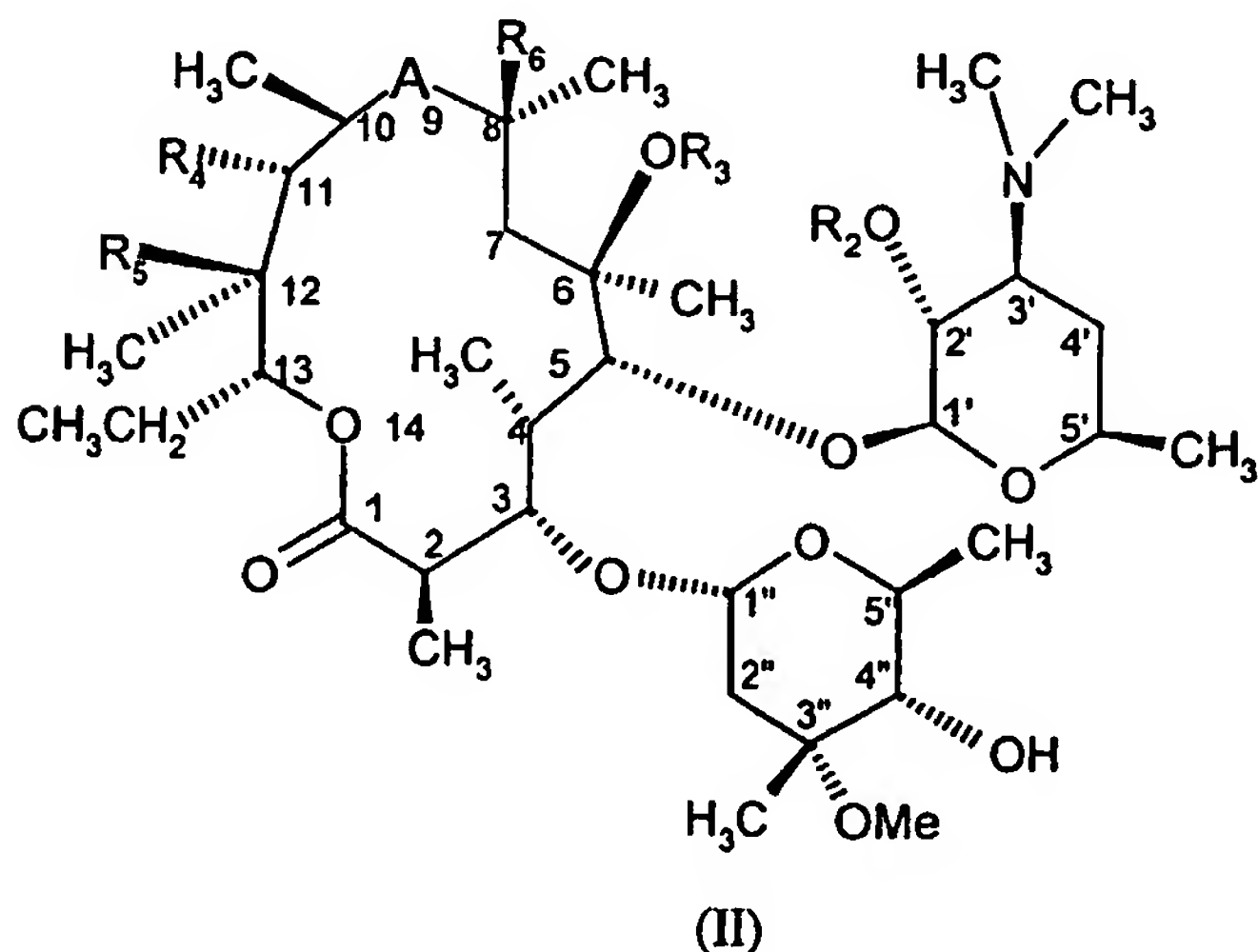
wherein R_9 , R_{10} , R_{11} and p are as defined in claim 1.

4. A compound according to claim 1 as defined in any one of Examples 1 to 119, or a pharmaceutically acceptable salt or solvate thereof.
5. A compound selected from
- 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A;
- 11,12-carbonate-4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyloxy)amino]ethyl]amino]propionyl]-11,12-dideoxy-azithromycin;
- 11,12-carbonate-4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyloxy)amino]ethyl]amino]propionyl]-11,12-dideoxy-azithromycin;
- 11,12-carbonate-4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyloxy)amino]ethyl]amino]propionyl]-11,12-dideoxy-azithromycin;
- 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyloxy)amino]ethyl]amino]propionyl]-azithromycin;
- 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyloxy)amino]ethyl]amino]propionyl]-11,12-dideoxy-11,12-(ethylaminocarbonyloxy)-6-O-methyl-erythromycin A;
- 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A;
- 4''-O-[3-[[2-[(3-carboxy-1,4-dihydro-1-ethyl-4-oxo-7-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A;
- 4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A;
- 4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyloxy)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A;
- (11*S*, 11*aR*)-4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyloxy)amino]ethyl]amino]propionyl]-11-(carboxycyanomethyl)-11-deoxy-6-O-methyl-erythromycin A;
- (11*S*, 11*aR*)-11-(carboxycyanomethyl)-4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyloxy)amino]ethyl]amino]propionyl]-11-deoxy-6-O-methyl-erythromycin A;

- 4''-O-[3-[4-(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-roxithromycin;
 4''-O-(3-(2-(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino)ethyl)-methyl-amino)propionyl)-11,12-dideoxy-11,12-(ethylaminocarbonyloxy)-6-O-methylerythromycin A;
 4''-O-{3-[(2-[(3-carboxymethyl-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl)amino]propionyl}-6-O-methyl-erythromycin A;
 11,12-(aminocarbonyloxy)-4''-O-{3-[(2-[(3-carboxy-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl)amino]propionyl}-11,12-dideoxy-6-O-methyl-erythromycin A;
 4''-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]-methyl-amino]propionyl]-azithromycin;
 11,12-carbonate-4''-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]-methylamino]propionyl]-11,12-dideoxy-azithromycin;
 4''-O-(3-{[2-(7-chloro-1-cyclopropyl-3-methoxycarbonyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethyl]-amino}-propionyl)-azithromycin;
 4''-O-(3-{[2-(7-chloro-1-cyclopropyl-3-methoxycarbonyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethyl]-methyl-amino}-propionyl)-azithromycin;
 4''-O-{3-[(2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl)methylamino]propionyl}-azithromycin; and
 4''-O-[3-[[2-[(3-carboxy-1-ethyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A.

6. A process for the preparation of a compound as claimed in claim 1 which comprises:

- a) reacting a compound of formula (II)



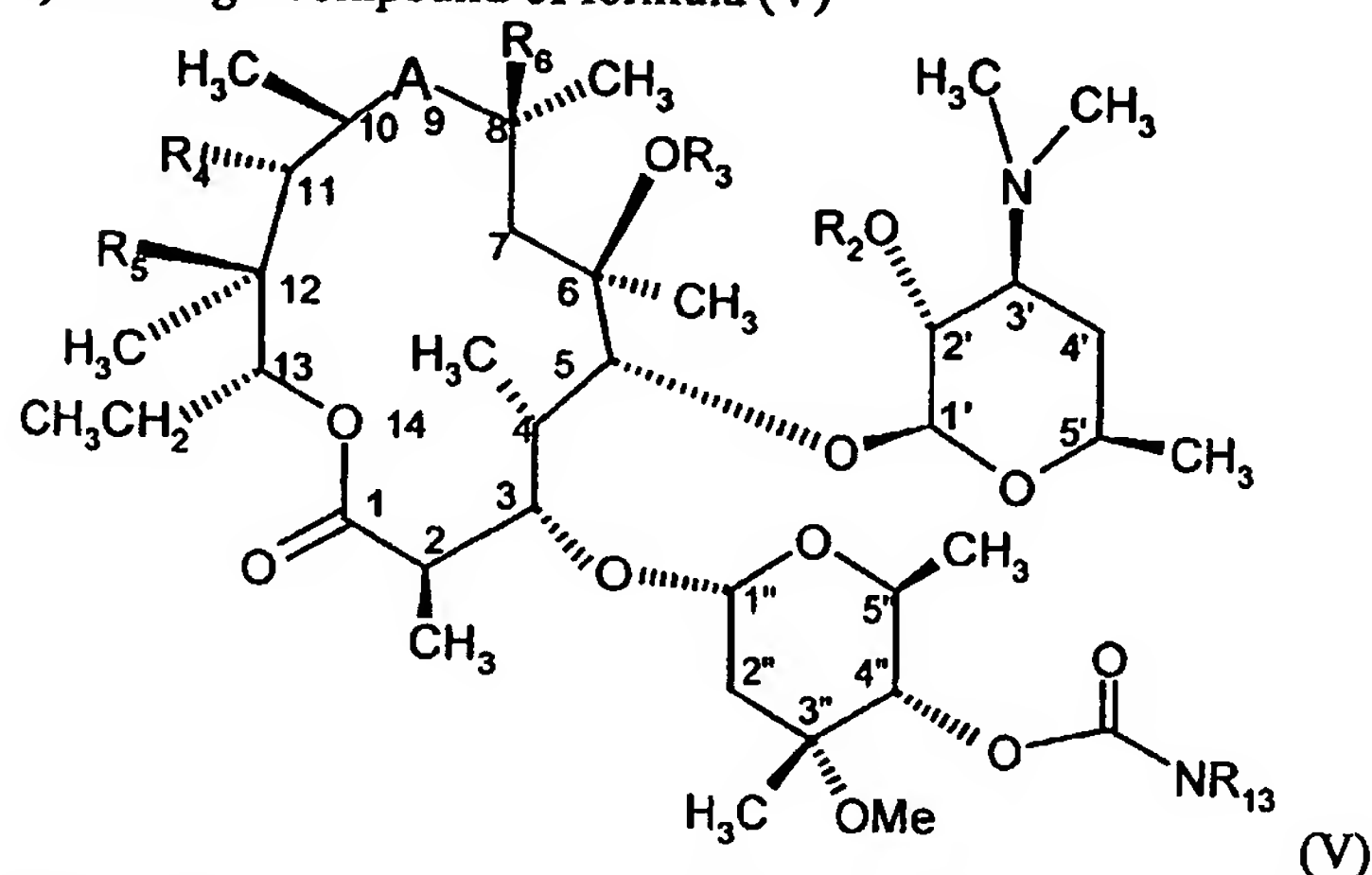
- with a suitable activated derivative of the acid (III), wherein n is an integer 1 to 5, X and R₇ have the meanings defined in claim 1, to produce a compound of formula(I) wherein n is an integer 1 to 5;

b) reacting a compound of formula (II), in which the 4'' hydroxy is suitable activated, with a compound of formula XR₇(IV), wherein R₇, m and Z have the meanings defined in claim 1 and X is -U(CH₂)_mZ-, in which U is a group selected from selected from:

-N(R₁₃)-, -O-, -S-,

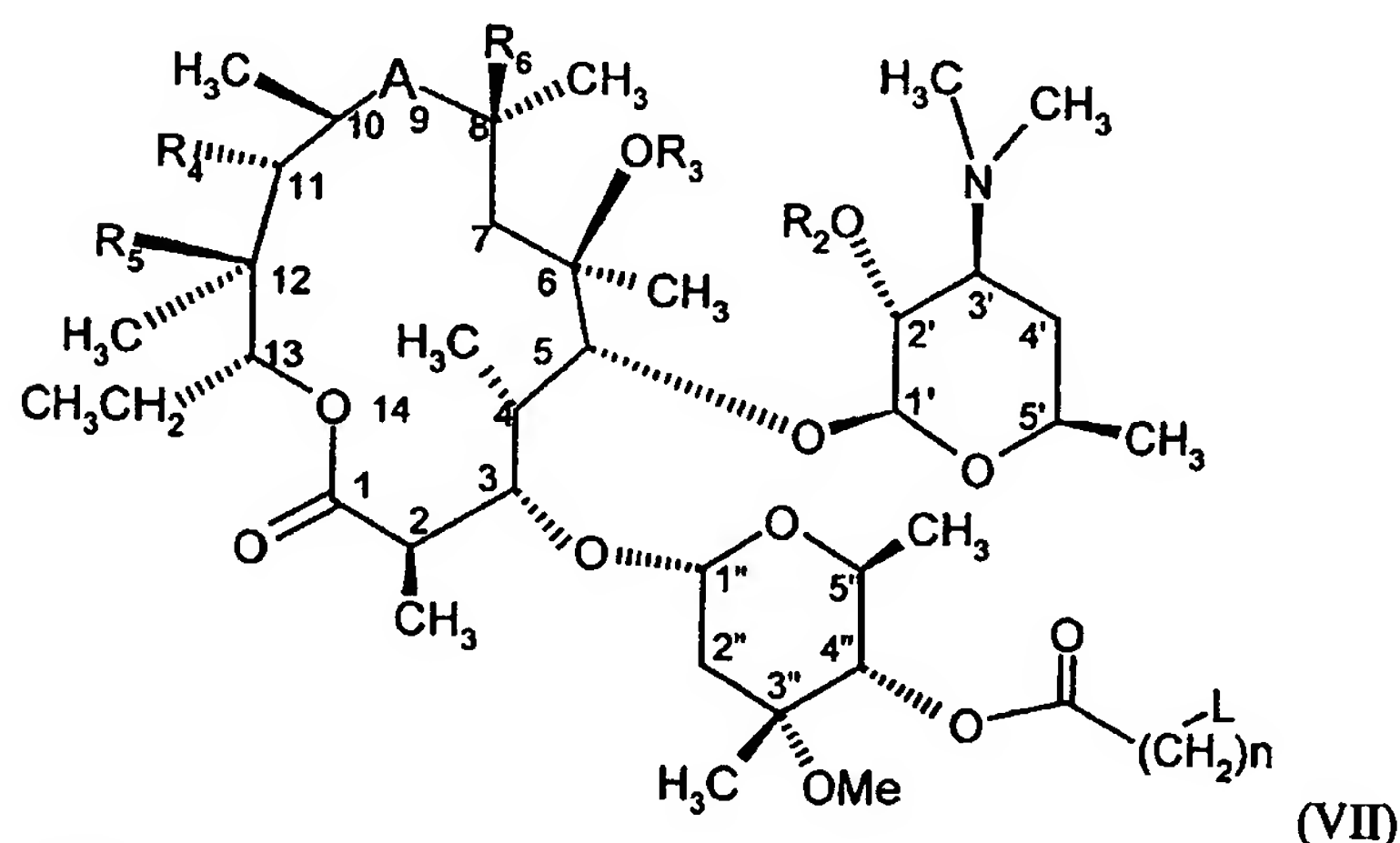
5 to produce a compound of formula (I) wherein n is 0 and U is a group selected from -N(R₁₃)-, -O-, -S-;

c) reacting a compound of formula (V)



10 wherein R₁₃ has the meaning defined in claim 1 with a suitable activated derivative of the carboxylic acid HOC(O)C(O)(CH₂)_mZR₇(VIIb), wherein R₇ and Z have the meanings defined in claim 1, to produce a compound of formula (I) wherein n is 0 and U is -N(R₁₃)C(O)-;

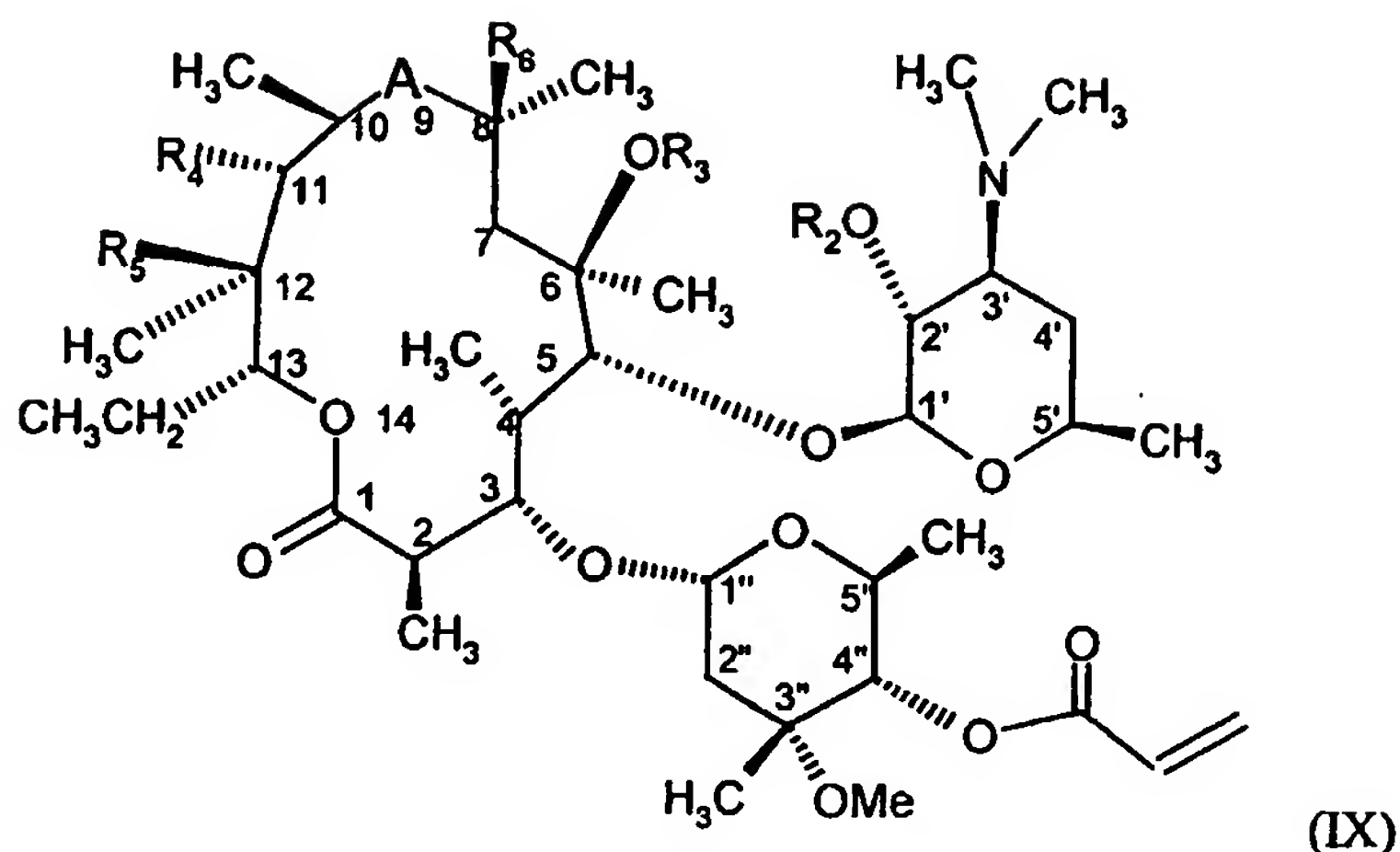
d) reacting a compound of formula (VII)



with a compound of formula XR_7 (IV), wherein R_7 and X have the meanings defined in claim 1 in which U is a group selected from $-\text{N}(\text{R}_{13})-$, $-\text{O}-$, $-\text{S}-$, and L is suitable leaving group, to produce a compound of formula (I) wherein n is 1 to 5 and U is a group selected from:

20 -N(R₁₃)-, -O-, -S-;

e) reacting a compound of formula (IX), with a compound of formula XR_7 (IV),



wherein R_7 and X have the meanings defined in claim 1, in which U is a group selected from $-N(R_{13})-$, $-O-$, $-S-$, to produce a compound of formula (I) wherein n is 2 and U is a group selected from:

$-N(R_{13})-$, $-O-$, $-S-$,

and thereafter, if required, subjecting the resulting compound to one or more of the following operations:

i) removal of the protecting group R_2 and

ii) conversion of the resultant compound of formula (I) into a pharmaceutically acceptable salt and solvates thereof.

7. A compound as claimed in any one of claims 1 to 5 for use in therapy.

8. The use of a compound as claimed in any one of claims 1 to 5 in the preparation of a medicament for use in the therapy of systemic or topical bacterial infections in a human or animal body.

9. The use of a compound as claimed in any one of claims 1 to 5 for use in the treatment or prophylaxis of systemic or topical bacterial infections in a human or animal body.

10. A pharmaceutical composition comprising a compound as claimed any one of claims 1 to 5 in admixture with one or more pharmaceutically acceptable carriers or excipients.

11. A method for the treatment of the human or non human animal body to combat bacterial infection comprising administration of an effective amount of a compound as claimed in any one of claims 1 to 5.

Internal Application No

PCT/GB 02/05101

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H17/08 A61K31/70 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 COZH

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 32917 A (GLAXO GROUP LTD ; ALIHODZIC SULEMAN (HR); BERDIK ANDREA (HR); DEREK) 25 April 2002 (2002-04-25) claim 1	1-11
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- *Z* document member of the same patent family

Date of the actual completion of the international search

3 February 2003

Date of mailing of the international search report

12/02/2003

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 02/05101

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>BAKER W R ET AL: "MODIFICATION OF MACROLIDE ANTIBIOTICS. SYNTHESIS OF 11-DEOXY-11- (CARBOXYAMINO)-6-OMICRON-METHYLERYTHROMYCI N A 11,12-(CYCLIC ESTERS)VIA AN INTRAMOLECULAR MICHAEL REACTION OF OMICRON-CARBAMATES WITH AN ALPHA,BETA-UNSATURATED KETONE" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 53, no. 10, 1988, pages 2340-2345, XP002026111 ISSN: 0022-3263 the whole document -----</p>	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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